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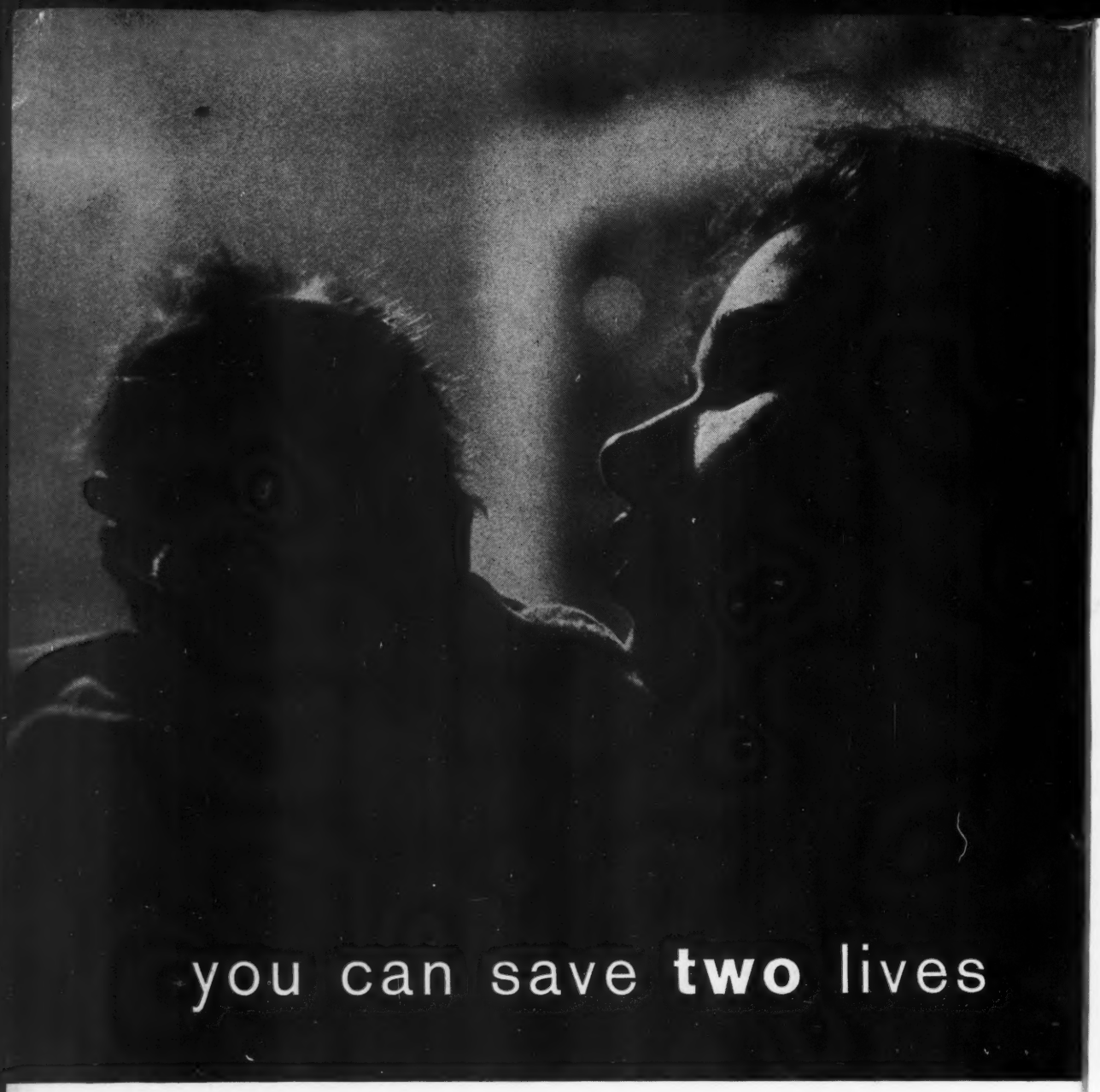

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CONTENTS

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OBSTETRICS

Shock

INTRA-ARTERIAL TRANSFUSION IN OBSTETRICS AND GYNECOLOGY
Conrad G. Collins, M.D., Frederick B. Jones, M.D., Winston H. Weese, M.D., John C. Thorn, M.D., and Frederick R. Braden, M.D., New Orleans, La. . . . 465

Labor

ELECTROMYOGRAPHY OF THE HUMAN UTERUS
E. L. Corey, Ph.D., Harry S. McGaughey, Jr., M.D., and W. Norman Thornton, Jr., M.D., Charlottesville, Va. 473

THE ENDOCRINE CONTROL OF MYOMETRIAL CONTRACTILITY IN THE UTERUS OF THE PREGNANT RABBIT
Lars Ph. Bengtsson, M.D., New York, N. Y. 484

MEASUREMENT OF THE MIDPELVIS WITH THE RECTOVAGINAL PELVIMETER TO MINIMIZE EXPOSURE TO RADIATION
Samuel Hanson, M.D., Stockton, Calif. 494

A NEW ADJUNCT TO ANALGESIA AND SEDATION IN LABOR
C. Donald Kuntze, M.D., and Patria Sison, M.D. 498

Placenta

PLACENTAL TRANSMISSION OF VIRUSES
Edith L. Potter, M.D., Chicago, Ill. 505

OBSERVATIONS ON THE FAILURE OF INSULIN TO PASS FROM THE FETUS TO THE MOTHER IN THE RABBIT
J. Davies, M.D., and Paul E. Lacy, M.D., St. Louis, Mo. 514

THE EFFECT OF PITOCIN ON THE PLACENTA
Lars Ph. Bengtsson, M.D., New York, N. Y. 518

Toxemia of Pregnancy

OPHTHALMODYNAMOMETRY IN TOXEMIAS OF PREGNANCY
Lalit P. Agarwal, M.B. (Luck.), D.O.M.S. (Eng.), D.O. (Oxon.), M.S. (Ophth.), S. R. Chawla, D.O.M.S., and R. P. Saxena, M.S. (Ophth.), Kanpur (U. P.), India 521

"NITROGENOUS RETENTION" IN PATIENTS WITH TOXEMIA OF PREGNANCY—AN UNUSUAL COMPLICATION OF SALT RESTRICTION
James G. Mulé, M.D., Howard J. Tatum, M.D., and Roy E. Sawyer, M.D., New Orleans, La. 526

ABO BLOOD GROUPS IN OBSTETRICS
Warren H. Pearse, M.D., Ann Arbor, Mich. 538

Miscellaneous

THE MANAGEMENT OF SECONDARY ABDOMINAL PREGNANCY
Lester T. Hibbard, M.D., Los Angeles, Calif. 543

CARBOHYDRATE METABOLISM IN PREGNANCY
Richard L. Burt, M.D., Winston-Salem, N. C. With the Technical Assistance of Nancy Julian, B.S. 551

A BIOCHEMICAL STUDY OF THE CERVICAL AND NASAL MUCUS FERN PHENOMENON
E. Himmat Abou-Shabanah, M.D., Columbus, Ohio, and Ernest J. Plotz, M.D., Chicago, Ill. 559

THE USE OF URECHOLINE IN THE PREVENTION OF POSTPARTUM URINARY RETENTION
A. R. Fleming, M.D., Baltimore, Md. 569

THE MOTHERS OF MONGOLOID BABIES: A RETROSPECTIVE APPRAISAL OF THEIR HEALTH DURING PREGNANCY
Theodore H. Ingalls, M.D., Joan Babbott, M.D., and Randolf Philbrook, M.D., Boston, Mass. 572

GYNECOLOGY

Menses

VARIATIONS IN BODY WEIGHT AND SALIVARY SODIUM IN THE MENSTRUAL CYCLE
Leon C. Chesley, Ph.D., and Louis M. Hellman, M.D., Brooklyn, N. Y. 582

TEEN-AGE DYSMENORRHEA
Leib J. Golub, M.D., Warren R. Lang, M.D., Hyman Menduke, Ph.D., and Hans C. Gordon, Ph.D., Philadelphia, Pa. 591

Cervix

DISSEMINATED GRANULOMA INGUINALE AND ITS RELATIONSHIP TO GRANULOMA OF THE CERVIX AND PREGNANCY
Walter B. V. Cherny, M.D., Claudius P. Jones, and Charles H. Peete, Jr., M.D., Durham, N. C. 597

CARCINOMA IN SITU AND THE ROLE OF CYTOLOGY IN ITS DETECTION
H. L. Riva, Colonel, MC, USA, W. L. Pickhardt, Lieutenant Colonel, MC, USA, and J. L. Breen, Captain, MC, USA 606

GLYCOGEN IN THE SQUAMOUS EPITHELIUM OF THE CERVIX UTERI
John S. Henry, Jr., M.D., and J. P. A. Latour, M.D., Montreal, Quebec . . . 610

RANDOM INGUINAL NODE BIOPSY AND PERITONEAL FLUID STUDY IN OVARIAN CANCER
Robert E. Cassidy, M.D., David P. Hansford, M.D., and R. Jocelyn Crawley, M.D., New Orleans, La. 616

Miscellaneous

POSTERIOR COLPOTOMY FOR THE DIAGNOSIS AND TREATMENT OF PELVIC DISEASE
Michael T. Daly, M.D., Philadelphia, Pa. 623

A SIMPLIFIED STAINING TECHNIQUE FOR THE STUDY OF CHROMOSOMAL SEX IN ORAL MUCOSAL AND PERIPHERAL BLOOD SMEARS
Robert B. Greenblatt, M.D., and Jorge Martinez Manautou, M.D., Augusta, Ga. With the Collaboration of N. R. Tigerman, B.S., R. L. Rogers, Jr., M.D., and F. H. Sheffield, M.D. 629

EXPERIMENTAL AND CLINICAL STUDIES ON A NEW SYNTHETIC ESTROGEN, AN ALLENOLIC ACID DERIVATIVE, VALLESTRIL
Hiroshi Furuya, M.D., Keiji Deguchi, M.D., and Motowo Shima, M.D., Tokyo, Japan 635

CASE REPORTS, NEW INSTRUMENTS AND METHODS

Obstetrics

PREGNANCY COMPLICATED BY NEPHROTIC SYNDROME
A. Charles Posner, M.D., Jack A. Goldman, M.D., and Geoffrey V. Forester, M.D., New York, N. Y. 651

PUERPERAL INVERSION OF THE UTERUS OCCURRING IN CONSECUTIVE PREGNANCIES IN THE SAME PATIENT
Elizabeth Allen Steffen, M.D., Racine, Wis. 655

MASSIVE RETROPERITONEAL HEMORRHAGE DUE TO RUPTURE OF OVARIAN VEIN FOLLOWING NORMAL DELIVERY
George B. German, M.D., E. A. Y. Schellenger, M.D., and Robert A. Haines, M.D., Camden, N. J. 658

PHOCOMELUS: A CASE OF CONGENITAL MALFORMATION
A. Charles Posner, M.D., Norman R. Bloch, M.D., and Bernard Green, M.D., New York, N. Y. 660

A CASE OF CRANIOSCHISIS WITH PLACENTAL ATTACHMENT TO THE DURA
A. Charles Posner, M.D., and Elie Shkolnik, M.D., New York, N. Y. 664

AN UNUSUALLY LARGE NONPATHOLOGICAL PLACENTA
Charles L. Chavigny, M.D., Portland, Ore. 667

A METHOD FOR DETERMINING THE PLASMA FIBRINOGEN TITER
Herbert S. Bowman, M.D., and Mary B. Yelito, Harrisburg, Pa. 670

DOES RETROPLACENTAL HEMATOMA CONTAIN FETAL BLOOD?
Yehuda M. Bromberg, M.D., Maccabi Salzberger, M.D., and Abraham Abrahamov, M.D., Jerusalem, Israel 674

Gynecology

POLYCYTHEMIA ASSOCIATED WITH UTERINE MYOMAS
Arthur R. Fleming, M.D., and John C. Markley, M.D., Gallipolis, Ohio . . . 677

CLINICAL NOTE ON THE USE OF INTRAVAGINAL TAMPONS DURING MENSTRUATION
Joseph B. Raddin, M.D., Phoenix, Ariz. 680

REVIEWS AND ABSTRACTS

REVIEWS OF NEW BOOKS 683
BOOKS RECEIVED 687
SELECTED ABSTRACTS 687

(See Page 8 for Editorial and Business Communications)

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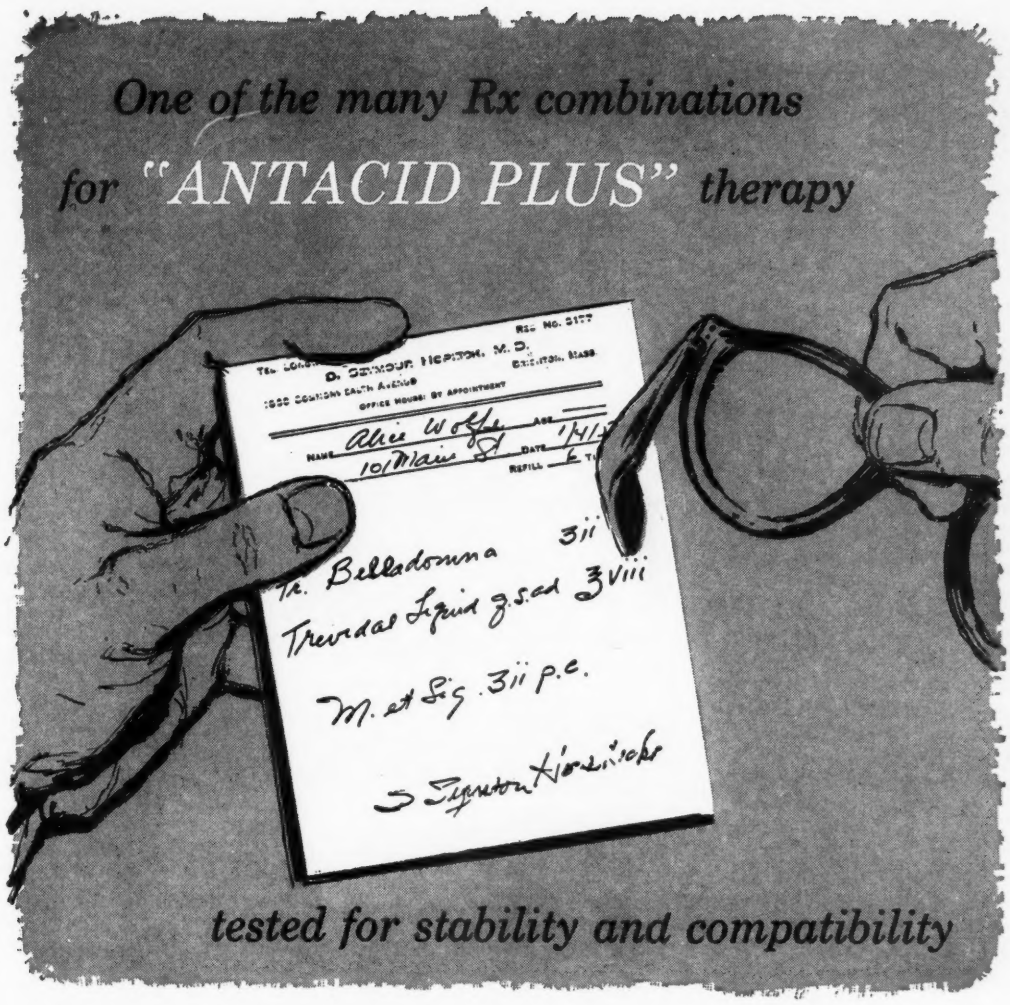
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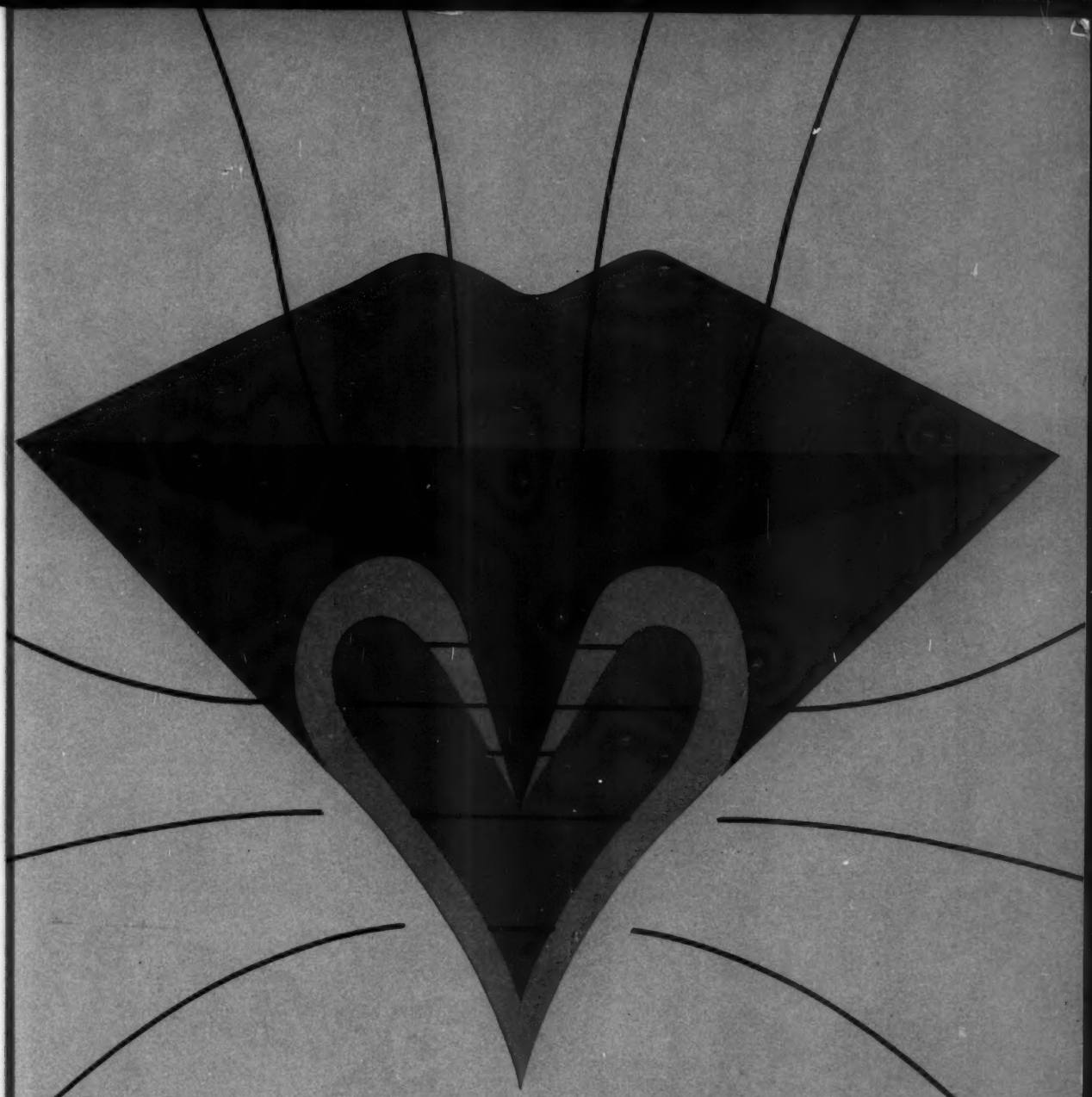

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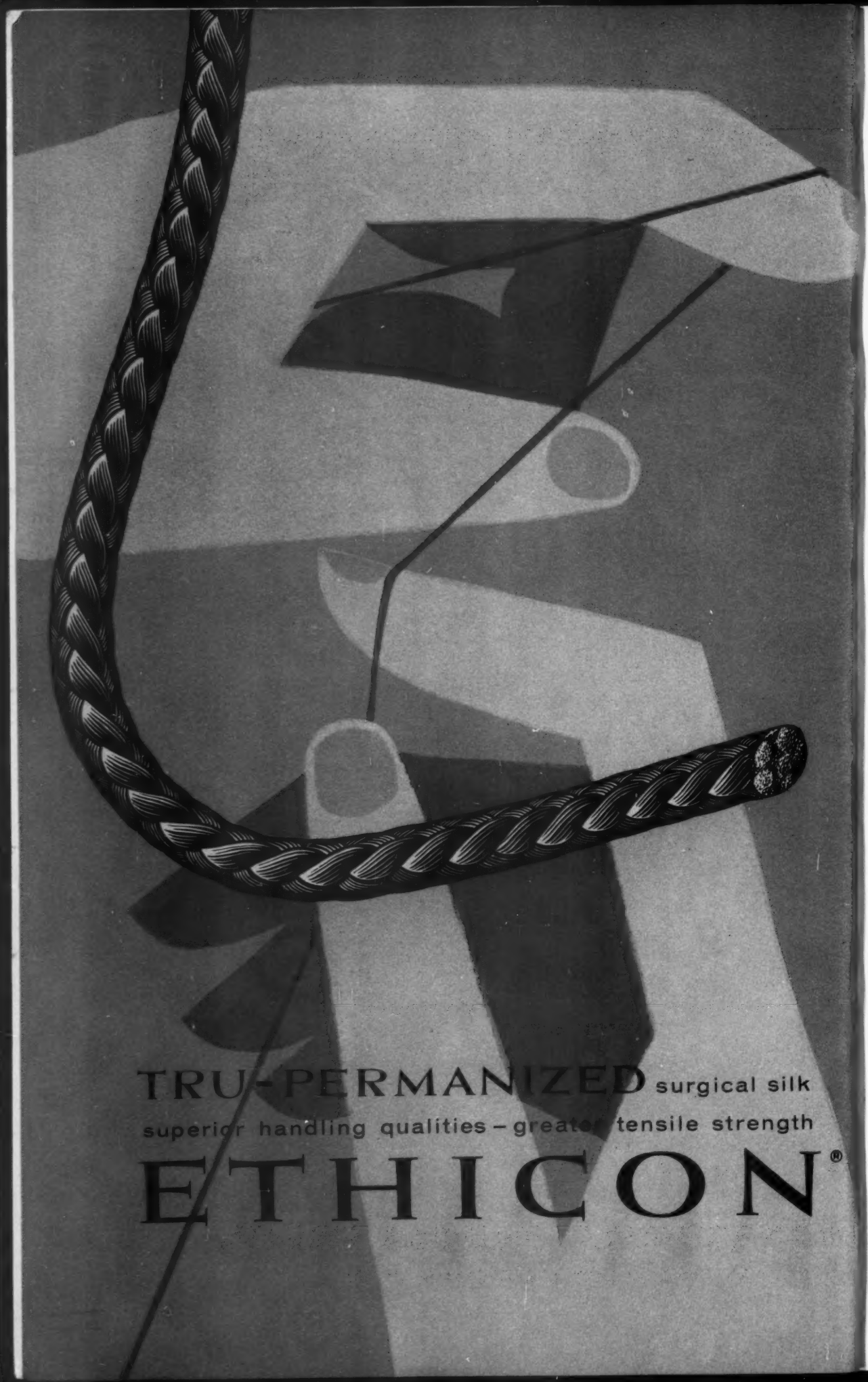
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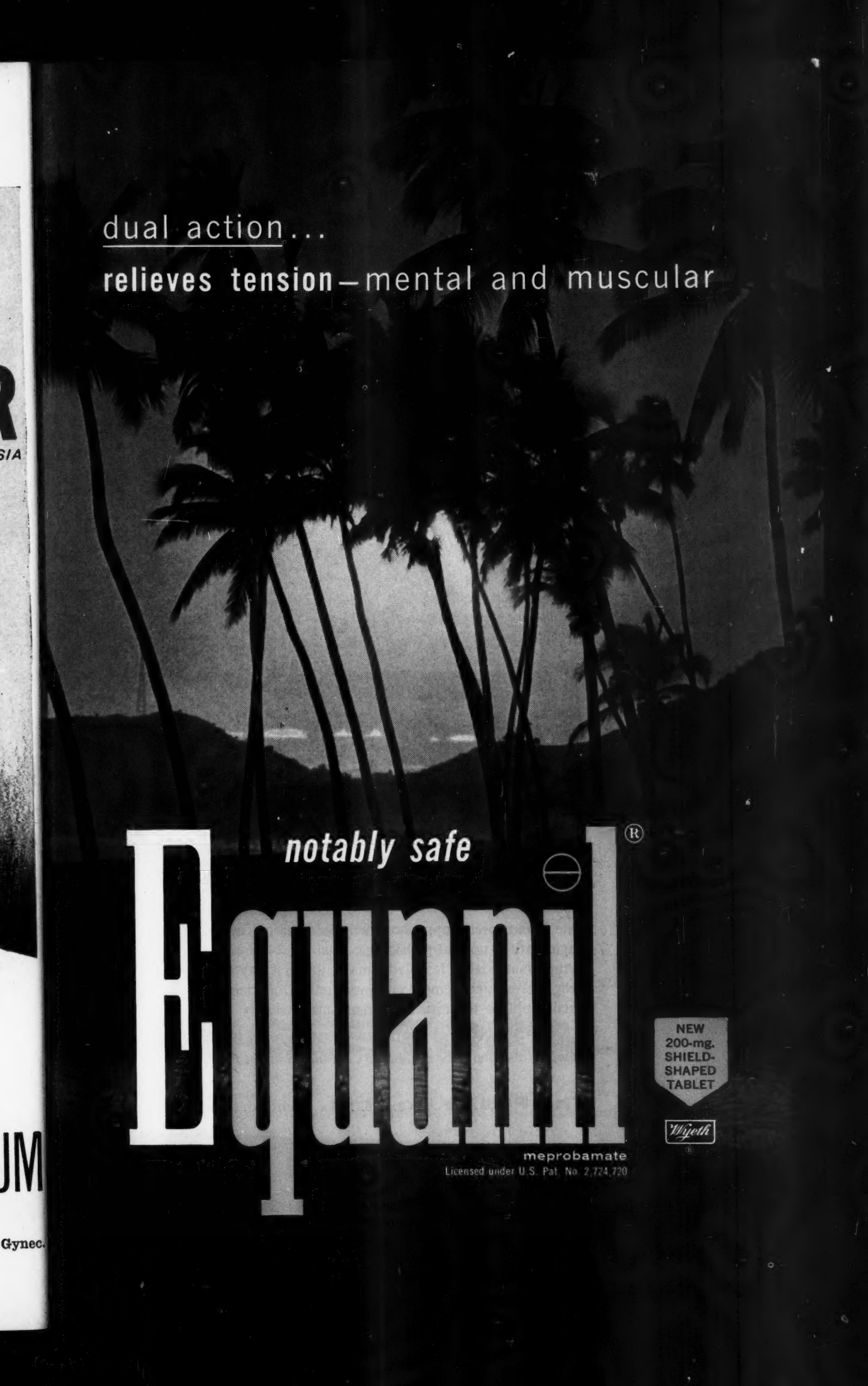
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Acting on the endometrium, the vaginal mucosa and the anterior pituitary, Enovid therapy has proved effective in the regulative control of such irregularities as primary and secondary amenorrhea[1-3], dysmenorrhea[4], prolonged or excessive menstrual bleeding[1,5] and distressing premenstrual tension[5].

INDICATIONS AND DOSAGE GUIDE FOR ENOVID

CONDITIONS	FIRST CYCLE	SECOND AND THIRD SUCCEEDING CYCLES
Amenorrhea (Primary or Secondary)	One tablet daily for 20 days to establish cycle	One tablet daily from day 5 to day 25*
Metrorrhagia	One or two tablets daily to day 25 or for 10 days to establish cycle†	Same as above
Menorrhagia	One or two tablets daily through balance of cycle†	Same as above
Oligomenorrhea	One tablet daily from day 5 to day 25*	Same as above
Dysmenorrhea	One tablet daily from day 5 to day 25‡	Same as above
Premenstrual Tension	One tablet daily from day 15 to day 25§	Same as for first cycle
Inadequate Luteal Phase	One tablet daily from day 15 to day 25	Same as for first cycle

*The administration of Enovid prior to day 15 may interfere with ovulation and if this is undesired, day 15 to day 25 may be substituted.

†If the patient is bleeding when first seen, two tablets will usually control the bleeding. In some patients less severe bleeding may be controlled with one tablet. The dosage used should be continued through the remainder of the cycle.

‡If dysmenorrhea is due to endometriosis, a special dosage schedule is required; Kistner[6] suggests 10 mg. daily for two weeks, 20 mg. daily for two weeks, 30 mg. daily for two weeks and 40 mg. daily for two to five months.

§Heller[5] recommends one tablet every twelve hours from day 5 to day 25 for two or three cycles.

REFERENCES:

1. Southam, A. L.; 2. Roland, M.; 3. Kupperman, H. S., and Epstein, J. A.; 4. Weinberg, C. H.: Papers Presented during a Symposium on Steroid Compounds Exhibiting Progestational Effects, Chicago, Searle Research Laboratories, January 23, 1957, to be published. 5. Heller, C. G.: Internat. Rec. Med. **169**:760 (November) 1956. 6. Kistner, R. W.: The Use of Newer Progestins in the Treatment of Endometriosis—A Pseudopregnancy, Section on Obstetrics and Gynecology, American Medical Association, New York, June 5, 1957.

FORMULA:

Each 10-mg. tablet of Enovid contains norethynodrel, a new synthetic steroid, and 0.15 of ethynylestradiol 3-methyl ether.

*TRADEMARK OF G. D. SEARLE & CO.

Supplied in uncoated, scored, coral-colored tablets.

G. D. Searle & Co., Chicago 80, Illinois.

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INTRODUCING
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"Milprem"—Miltown® + Conjugated Estrogens (equine)—combines for complementary action a *proven* tranquilizer with a *proven* natural estrogen for simultaneous control of *both* manifestations of the menopause—the psychologic and physiologic.

"Milprem" restores emotional *and* hormonal balance in menopausal distress.

"Milprem" represents, therefore, rational and comprehensive menopausal therapy. With *one* prescription you can now safely manage the *whole* menopausal syndrome. Samples and literature on request.

For two-dimensional treatment of the menopause

Supplied: Bottles of 60 tablets.
Each tablet contains:

MILTOWN® (meprobamate, Wallace) ..... **400 mg.**
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U. S. Patent No. 2,724,720.

Conjugated Estrogens (equine) ..... **0.4 mg.**
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Dosage: One tablet t.i.d. in 21-day courses with one week rest periods.
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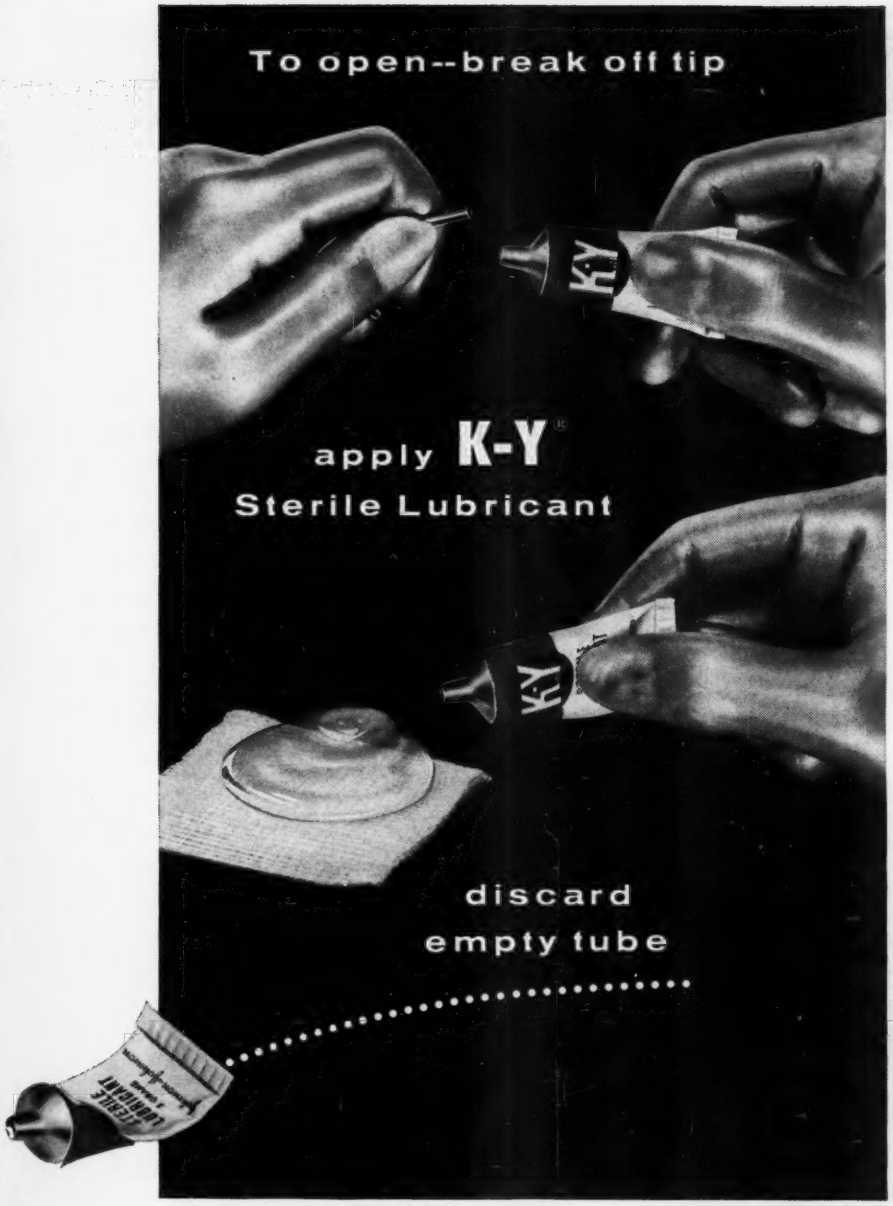

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Hesper-C Prenatal

with capillary-protective factors

a precaution in normal pregnancy *a necessity* in habitual abortion[1,2]

The problem of spontaneous abortion is not limited to habitual aborters. It is estimated that 10% to 20% of *all* pregnancies end in spontaneous abortion. Studies by Greenblatt,[1,3] Javert[4,5] and Dill[2] have revealed that integrity of the decidual vessels is a key to successful completion of pregnancy . . . and confirm that hesperidin complex and ascorbic acid, provided by Hesper-C Prenatal, restore and maintain capillary integrity.[6,7]

In several groups of habitual aborters, these researchers effected substantial fetal salvage—as high as 95% in one series[4]—when Hesper-C (hesperidin complex and ascorbic acid) was added to a regimen of prenatal supplementation and therapy.

Only Hesper-C Prenatal gives your patients the extra protection of hesperidin complex and ascorbic acid, plus the established prenatal vitamin-mineral supplementation, at a nominal increase in daily cost.

Hesper-C Prenatal is the only *complete* supplement for *all* your pregnant patients.

Each capsule contains:

Hesperidin Complex	100 mg.	Vitamin B_{12}	0.75 micrograms
Ascorbic Acid	100 mg.	Folic Acid	0.05 mg.
Vitamin A Acetate	1000 U.S.P. units	Pyridoxine Hydrochloride	1.67 mg.
Vitamin D_2	200 U.S.P. units	Calcium Pantothenate	1.0 mg.
Thiamine Mononitrate	1.25 mg.	Ferrous Gluconate (2.5 mg. iron)	21.6 mg.
Riboflavin	0.75 mg.	Calcium Carbonate (83.3 mg. calcium)	208.25 mg.
Nicotinamide	5.0 mg.	Copper Sulfate (0.5 mg. copper)	2.0 mg.
		Potassium Iodide (0.05 mg. iodine)	0.065 mg.

In bottles of 100 and 500 capsules.

Recommended daily dose: Two capsules t.i.d.
Providing the daily requirements or more of vitamins and iron during pregnancy as recommended by the National Research Council.

References: 1. Greenblatt, R. B.: Obst. & Gynec. *2*:530, 1953. 2. Dill, L. V.: M. Ann. District of Columbia *23*:667, 1954. 3. Greenblatt, R. B.: Ann. New York Acad. Sc. *61*:713, 1955. 4. Javert, C. T.: Obst. & Gynec. *3*:420, 1954. 5. Javert, C. T.: Ann. New York Acad. Sc. *61*:700, 1955. 6. Barishaw, S. B.: Exp. Med. & Surg. *7*:358, 1949. 7. Selsman, G. J. V., and Horoschak, S.: Am. J. Digest. Dis. *17*:92, 1950.

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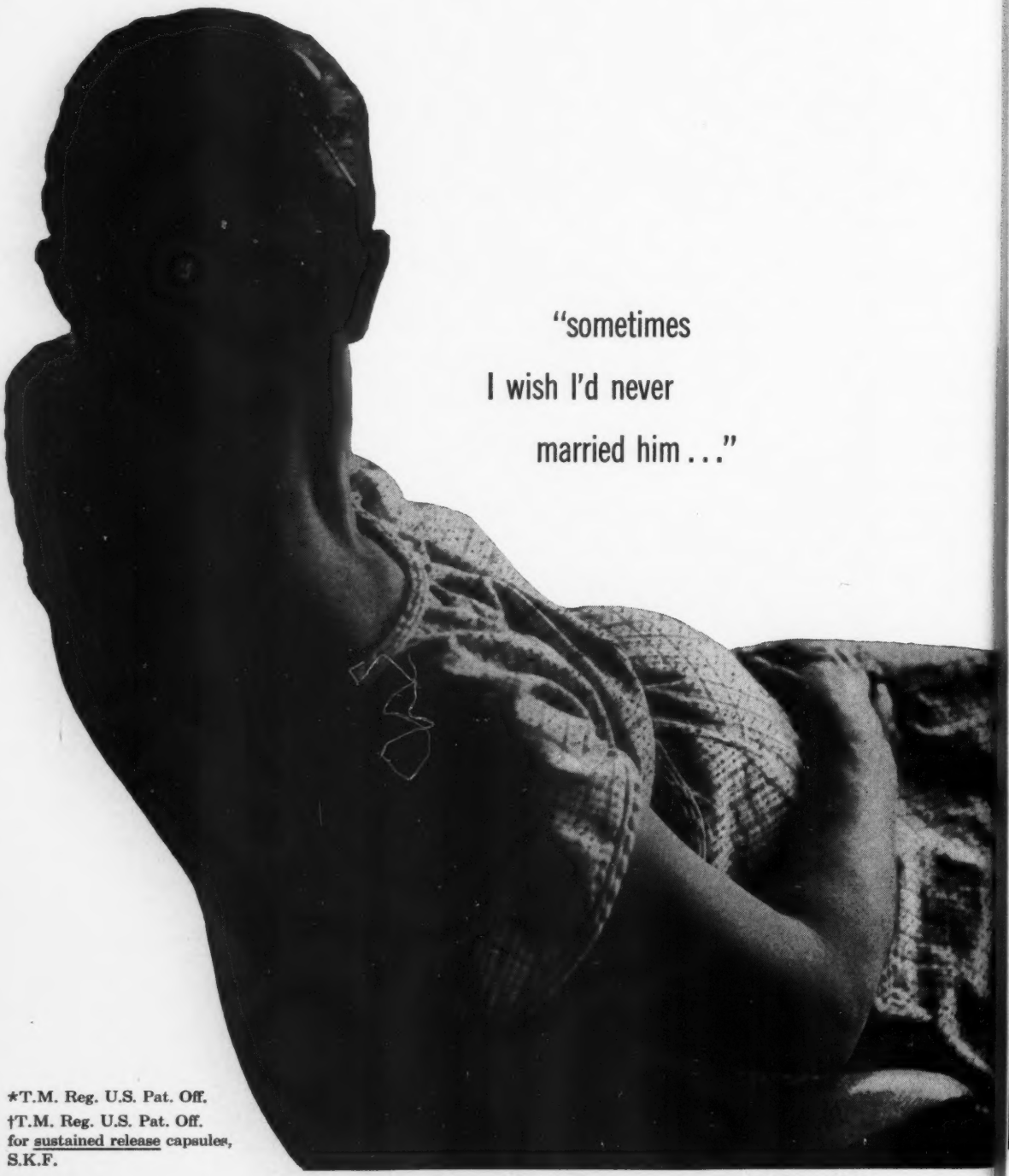

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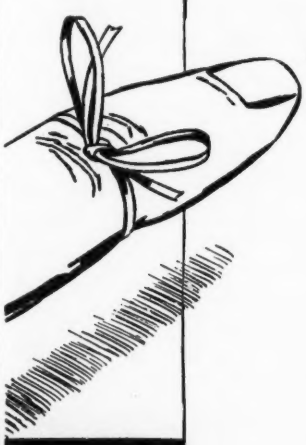

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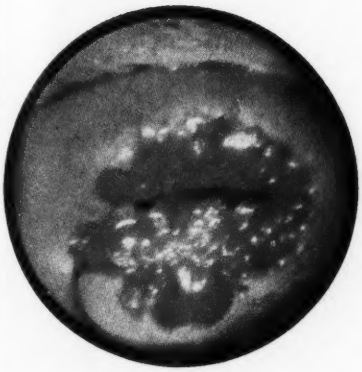
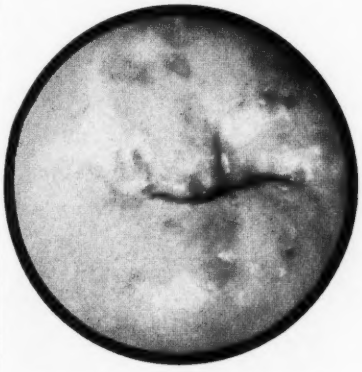
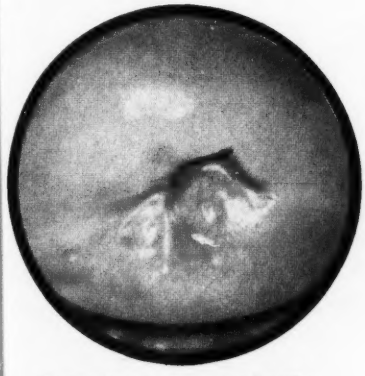


Pre-cauterization



2 weeks post-cauterization



3 weeks post-cauterization, healing nearly complete

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Whether cauterization, conization, other surgical operation or radiation of the cervix uteri is indicated, FURACIN Vaginal Suppositories can aid materially. Administered before and after these procedures, they eliminate infection; minimize discharge, malodor and irritation; facilitate healing and provide a more rapid and comfortable convalescence. In conjunction with radiotherapy, they control infection and thus contribute to "a better response of the malignant tissue to a given unit of radiation."* FURACIN Vaginal Suppositories do not cause monilial superinfection and are safe for prolonged use.

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*Schwartz, J., and Nardiello, V.: Am. J. Obst. 65:1069, 1953.

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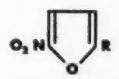

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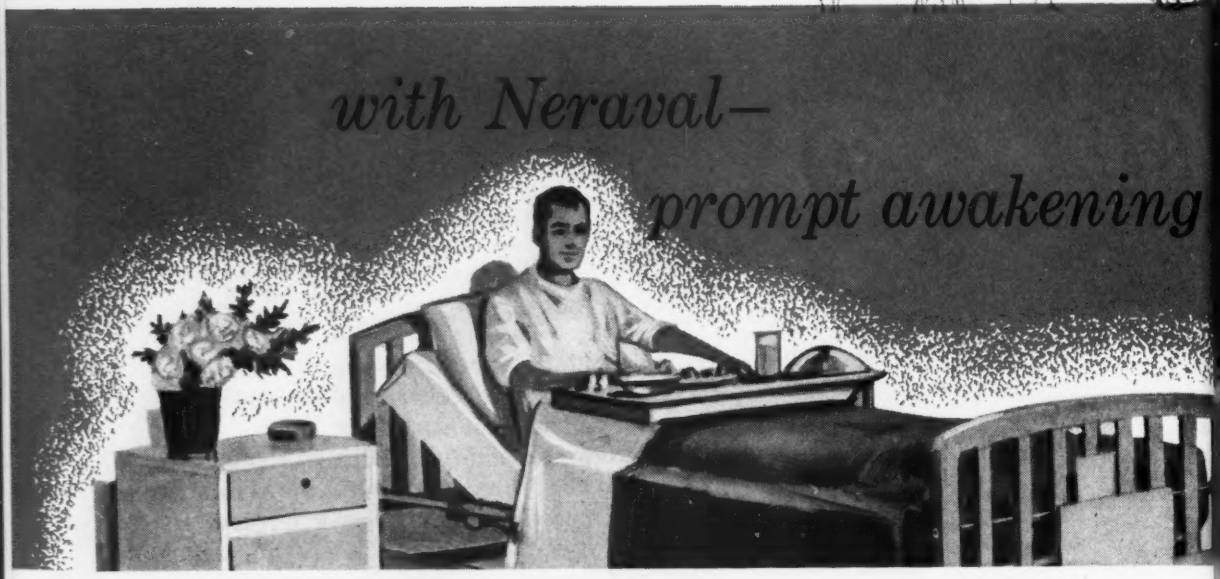

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and many other situations in which advantageous use can be made of "...the shortest-acting thiobarbiturate so far.

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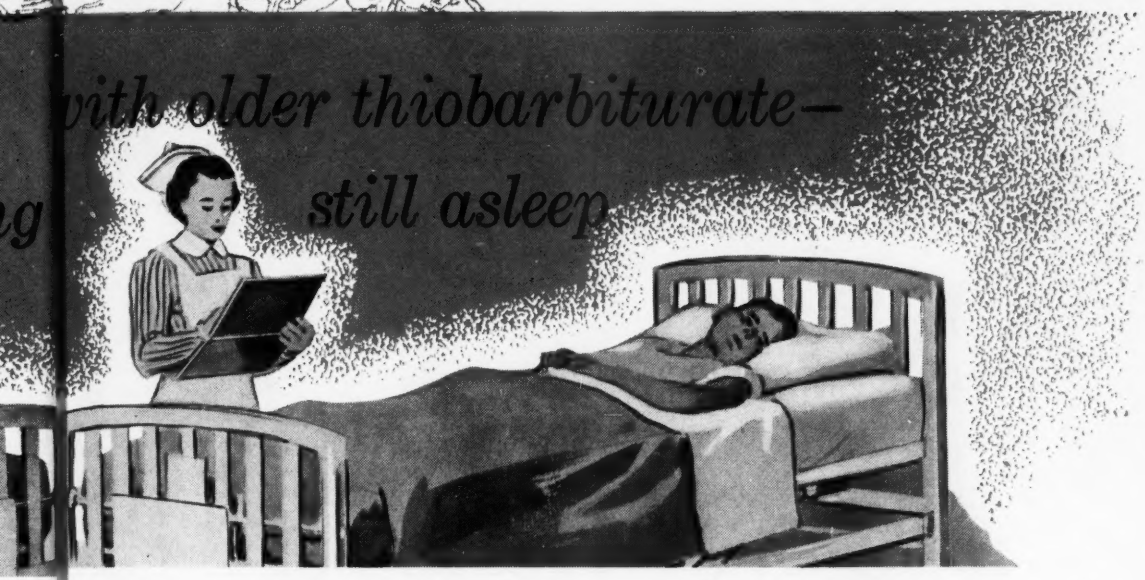

.distinctive among thiobarbiturates r its briefer action and sser tendency to accumulation

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Bibliography:
(1) Boone, J. D.; Muñoz, R., and Dillon, J. B.: Anesthesiology *17*:284, 1956. (2) Zima, O.; von Werder, F., and Hotovy, R.: Anaesthesist *3*:244, 1954. (3) Mersch, M. A.; Clarie, D'A., and Fitzpatrick, L. J.: J.M. Soc. New Jersey *53*:414, 1956. (4) Blake, M. W., and Perlman, P. L.: J. Pharmacol. & Exper. Therap. *117*:287, 1956. (5) Irwin, S.; Stagg, R. D. Dunbar, E., and Govier, W. M.: J. Pharmacol. & Exper. Therap. *116*:317, 1956. (6) Ayd, F. J., Jr.: Neraval: A new anesthetic for electroconvulsive therapy, Paper presented at annual meet., Electroshock Research Association, Chicago, Illinois, April 29, 1956. (7) Reifferscheid, M., and Dietmann, K.: Deutsche med. Wchnschr. *79*:638, 1954. (8) Houde, J., Hudon, F., and Jacques, A.: Neraval (methitural sodium), Paper presented at Meet., Canad. Anaesth. Soc., Quebec City, P. Q., May 5, 1956.

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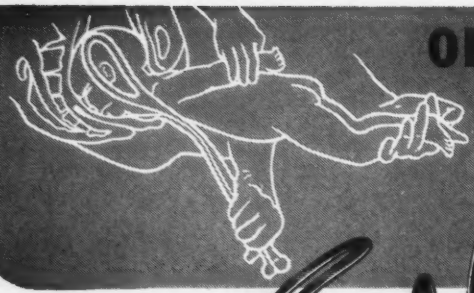

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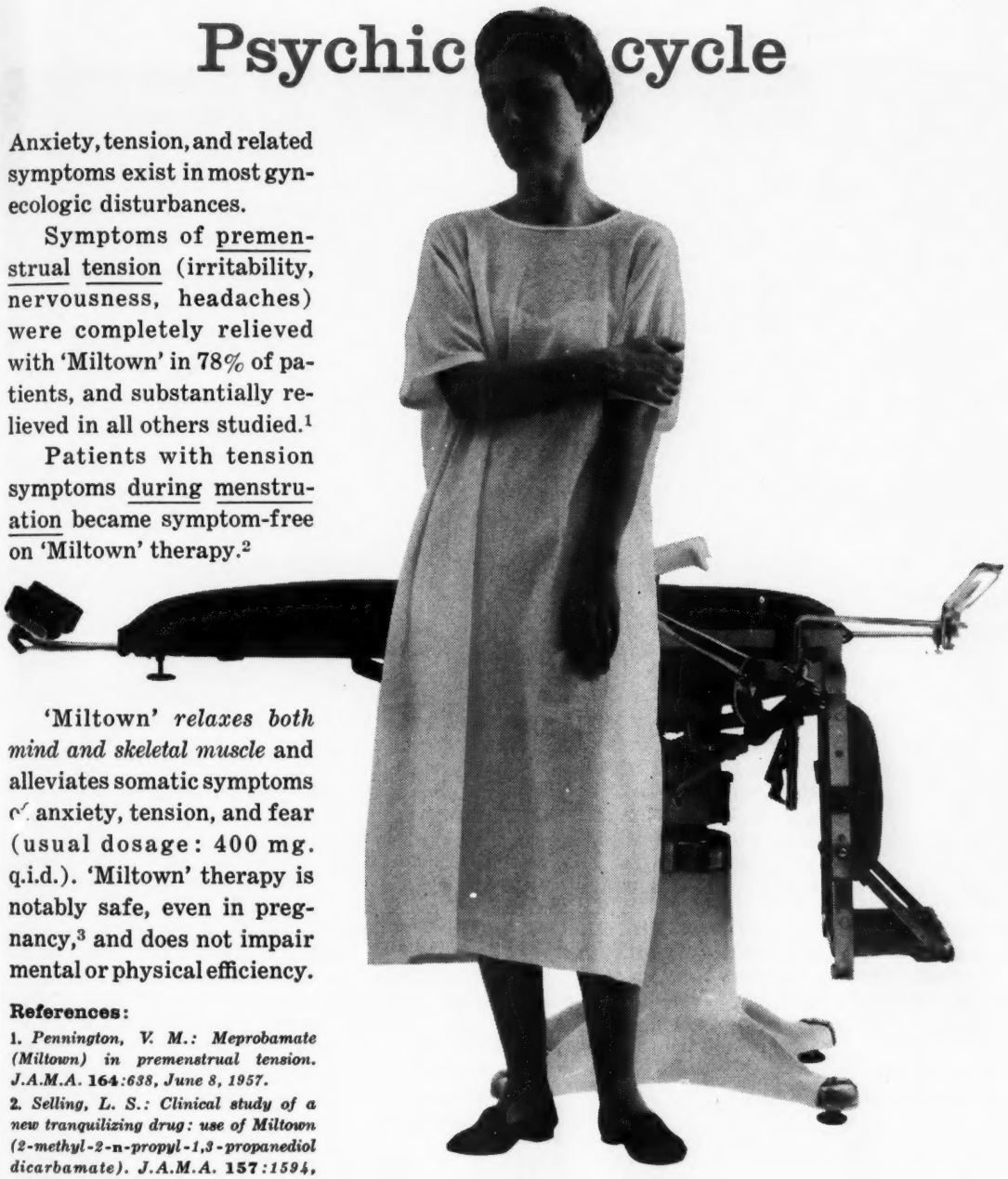

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Symptoms of premenstrual tension (irritability, nervousness, headaches) were completely relieved with 'Miltown' in 78% of patients, and substantially relieved in all others studied.[1]

Patients with tension symptoms during menstruation became symptom-free on 'Miltown' therapy.[2]

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References:

1. *Pennington, V. M.: Meprobamate (Miltown) in premenstrual tension. J.A.M.A.* **164**:*638, June 8, 1957.*
2. *Selling, L. S.: Clinical study of a new tranquilizing drug: use of Miltown (2-methyl-2-n-propyl-1,3-propanediol dicarbamate). J.A.M.A.* **157**:*1594, April 30, 1955.*
3. *Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gyn.* **9**:*703, June 1957.*

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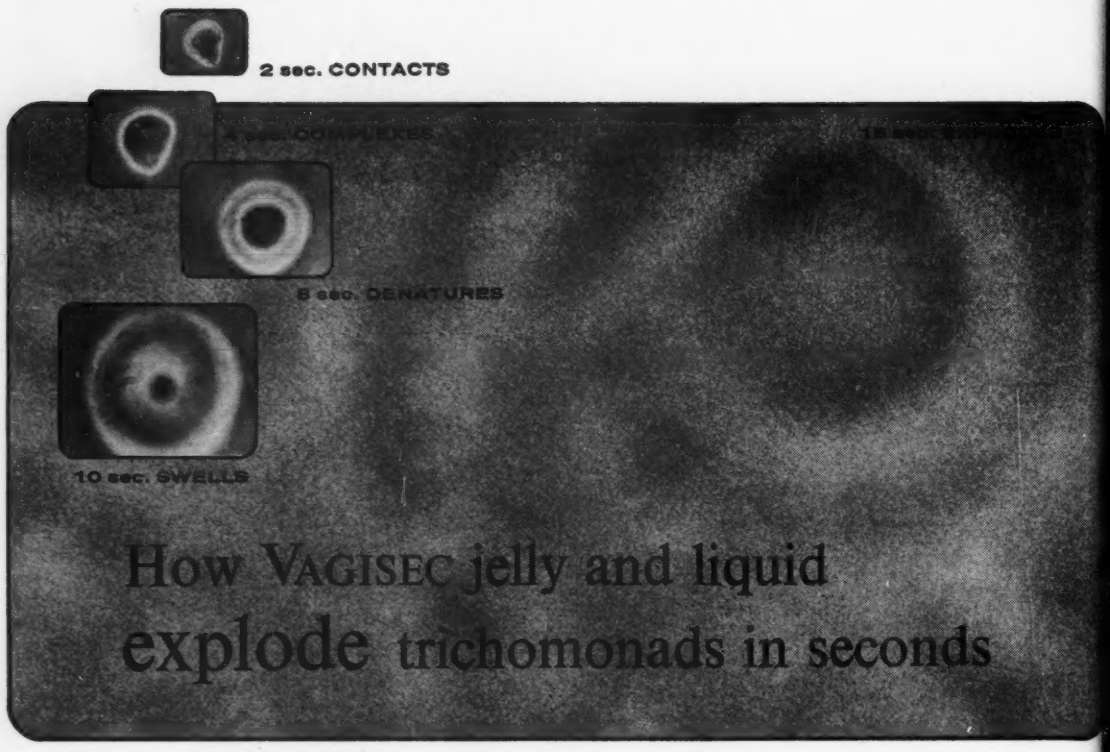

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VAGINAL trichomoniasis quickly yields to VAGISEC® liquid and jelly.[1-5] These unique trichomonacides *explode* flagellates after 15 seconds' contact. Following a VAGISEC douche, VAGISEC jelly maintains trichomonacidal effectiveness 'round-the-clock. With this new approach, therapy succeeds in more than 90 per cent of cases.[4]

Research proves effectiveness — In hundreds of tests with slide preparations, mixtures of VAGISEC jelly and vigorous cultures of *Trichomonas vaginalis* have been examined under a phase-contrast microscope.[3,6] The trichomonads *explode and disperse within 15 seconds* after contact with jelly — exactly like those in a VAGISEC douche solution.[3-6]

Explosion succeeds — VAGISEC liquid and jelly penetrate rapidly to trichomonads covered by vaginal mucus and cellular debris and *explode* them, avoiding post-treatment flare-ups.[3-5] VAGISEC therapy often rids stubborn clinical cases of "trich" even after other agents fail.

Why parasites explode — A wetting agent, a detergent and a chelating agent, combined in balanced blend in VAGISEC liquid and jelly,[3-5] act to weaken the parasites' cell membranes, remove waxes and lipids, and denature the protein. Then the trichomonads imbibe water, swell and explode into fragments . . . all within 15 seconds.

The Davis technique† — Dr. Carl Henry Davis, co-discoverer of VAGISEC, recommends a combination of office treatments with VAGISEC liquid and 'round-the-clock home therapy with the liquid and jelly.[3] This regimen halts vaginal trichomonal infections and ensures *continuous* control until all trichomonads are gone. For a small percentage of women who have an involvement of cervical, vestibular or urethral glands, other treatment will be required.[1,3-5]

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References: 1. Decker, A., and Decker, W. H.: Practical Office Gynecology, Philadelphia, F. A. Davis Company, 1956. 2. McGoogan, L. S.: J. Michigan M. Soc. *55*:682 (June) 1956. 3. Davis, C. H. (Ed.): Gynecology and Obstetrics (revision), Hagerstown, W. F. Prior, 1955, vol. 3, chap. 7, pp. 23-33. 4. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955. 5. Davis, C. H.: J.A.M.A. *157*:126 (Jan. 8) 1955. 6. Molomut, N., Port Washington, N. Y.: Personal communication (Jan.) 1957. 7. Draper, J. W.: Internat. Rec. Med. *168*:563 (Sept). 1955. 8. Feo, L. G., et al.: J. Urol. *75*:711 (Apr.) 1956.

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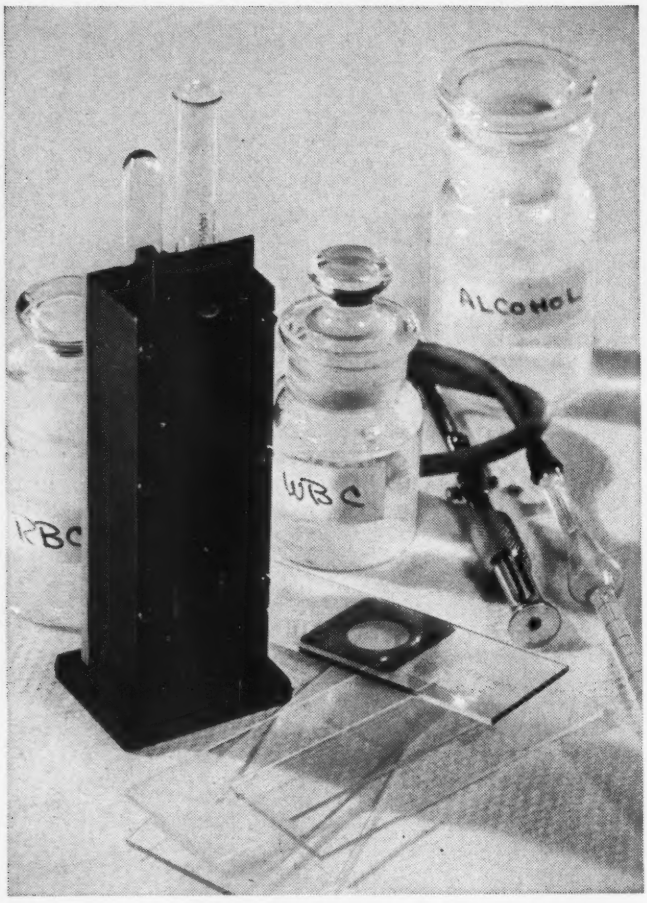

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* **Times Square's** largest sign isn't big enough to cover all the pages of scientific reports published on GANTRISIN.

The efficacy of GANTRISIN as an antibacterial agent is recognized everywhere. Of its ten forms it can be said that each provides an action against infections that is decisive, rapid, enduring and, above all, safe.

Lipo gantrisin
for infections
in children —

LIPO GANTRISIN

'ROCHE'

provides therapeutic blood levels of time-proved Gantrisin around-the-clock—with only two doses daily

DESCRIPTION:

Lipo Gantrisin should be considered for use in many systemic and urinary tract infections because it provides:

1. the time-proved wide-spectrum antibacterial action of Gantrisin in a stable, free-flowing homogenized emulsion
2. convenience of therapeutic blood levels for 24 hours with just two daily doses
3. delicious taste that assures wide acceptance by children and adults
4. no need for forced fluids . . . no danger of renal blocking or secondary fungus growth

INDICATIONS:

Systemic and urinary tract infections due to streptococci, staphylococci, pneumococci, H. influenzae, K. pneumoniae, meningococci, E. coli, B. proteus, B. pyocyaneus, A. aerogenes, B. paracolon and Alcaligenes fecalis.

DOSAGE:

Children:	teaspoonfuls every 12 hours
20 lbs	1
40 lbs	1½
60 lbs	2
80 lbs	3
Adults:	4

CAUTION:
The usual precautions in sulfonamide therapy should be observed.

SUPPLIED:

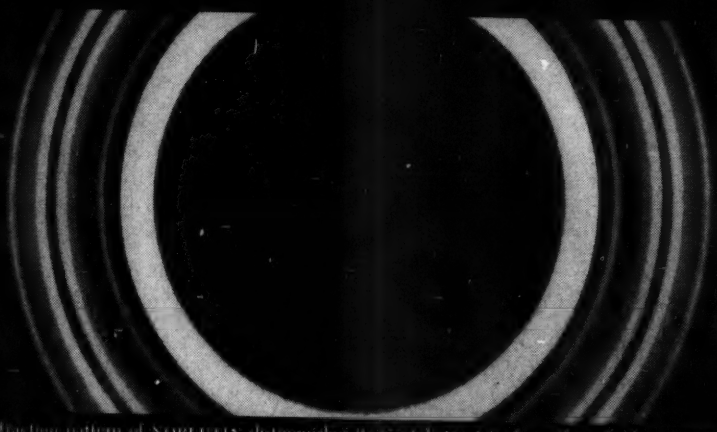
Lipo Gantrisin Acetyl, containing 20 per cent Gantrisin (1 Gm per 5 cc in the form of Gantrisin Acetyl), in a palatable, readily digestible homogenized emulsion that prolongs the action of the drug. In bottles of 4 and 16 oz.

Lipo Gantrisin® Acetyl – brand of acetyl sulfisoxazole

ROCHE

HOFFMANN - LA ROCHE INC • NUTLEY • N. J.

PARKE-DAVIS ANNOUNCES A MAJOR ADVANCE IN FEMALE HORMONE THERAPY



▲ The X-ray diffraction pattern of NORLUTIN distinguishes its crystal structure from that of other progestogens.

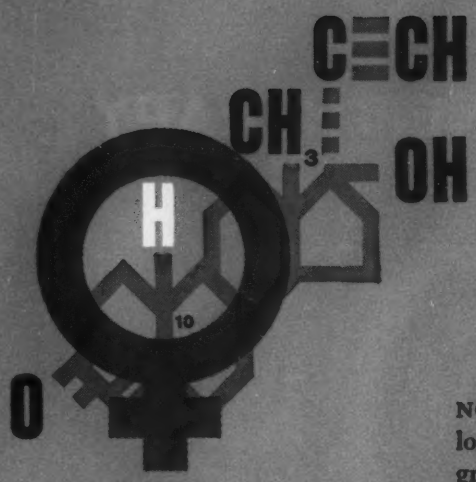
NORLUTIN ™

(norethindrone, Parke-Davis)

oral progestational agent with unequalled potency and unsurpassed efficacy

UNEQUALLED POTENCY

for oral progestational therapy



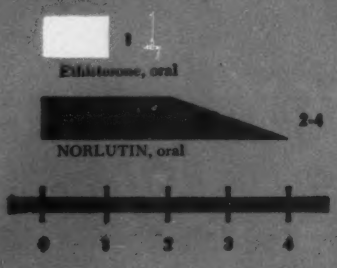
NORLUTIN
(17-alpha-ethinyl-19-nortestosterone)

NORLUTIN is an example of "...increased biological activity of a steroid when the methyl group at carbon 10 is replaced with hydrogen."[1]

NORLUTIN

INDICATIONS FOR NORLUTIN: amenorrhea, menstrual irregularity, functional uterine bleeding, infertility, habitual abortion, threatened abortion, premenstrual tension, dysmenorrhea.

RELATIVE POTENCIES OF ETHISTERONE AND NORLUTIN IN HUMANS[2, 3]

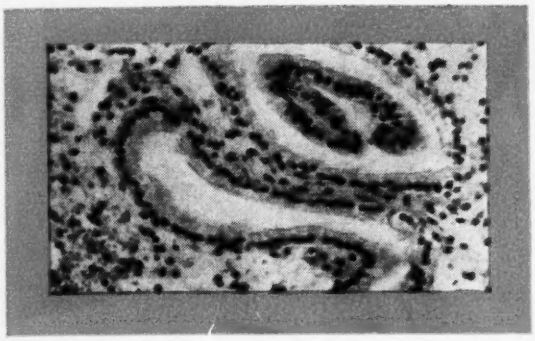


REFERENCES: (1) Hertz, R.; Tullner, W., & Raffelt, E.: *Endocrinology* 54:228, 1954. (2) Greenblatt, R. B.: *J. Clin. Endocrinol.* 16:869, 1956. (3) Hertz, R.; Waite, J. H., & Thomas, L. B.: *Proc. Soc. Exper. Biol. & Med.* 91:418, 1956. (4) Tyler, E. T.: *J. Clin. Endocrinol.* 15:881, 1955. (5) Greenblatt, R. B., & Clark, S. L.: M. Clin. North America, Philadelphia, W. B. Saunders Co. (Mar.) 1957, p. 587.

PACKAGING: 5 mg. scored tablets (C. T. No. 882), bottles of 30.

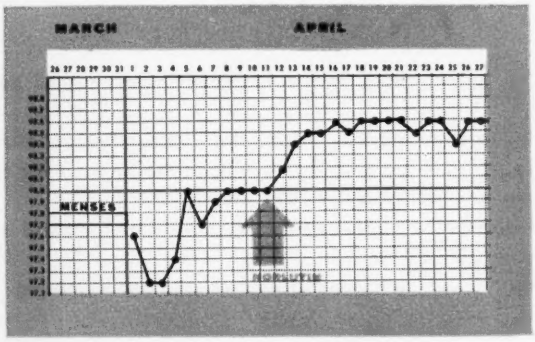
UNSURPASSED EFFICACY

in disorders of menstruation and pregnancy

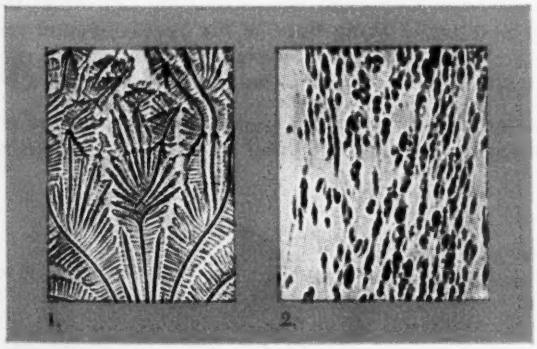


NORLUTIN: **Progestational Effect on Endometrium**"...10 mg. [NORLUTIN] given twice daily represents a reproducibly effective dose in women for the production of marked progestational changes in the endometrium."[3]

Presecretory to secretory endometrium after 5 days treatment.



NORLUTIN: **Thermogenic Effect** "This preparation was found to have a marked thermogenic, and other physiologic effects in comparatively small dosage."[4]



NORLUTIN: **Abolition of Arborization in Cervical Mucus** NORLUTIN "...inhibits the fern leaf pattern in cervical mucus."[5]

1. Fern leaf pattern. 2. Arborization completely abolished by NORLUTIN.

NORLUTIN: **Induction of Withdrawal Bleeding** "As little as 50 mg. of [NORLUTIN] administered in divided doses over a five-day period was sufficient to induce withdrawal bleeding."[2]

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

50172

SAVES TEACHING TIME...

Koro-Flex
TRADE MARK

improved

THE DIAPHRAGM WITH THE

CONTOURING SPRING (ARCING TYPE)

SIX REASONS WHY PHYSICIANS ARE RECOMMENDING Koro-Flex
TRADE MARK

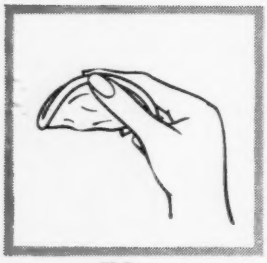


FIG. 1

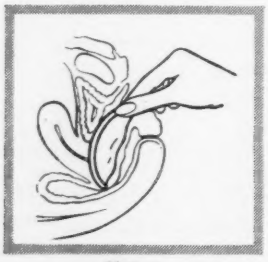


FIG. 2

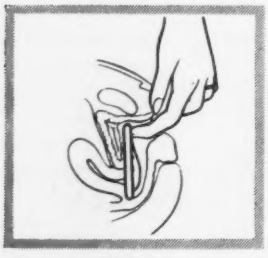


FIG. 3

1. Expressly designed to assure your patient ease of insertion and automatic placement.
2. Conserves physician's time by reducing fitting and instruction period.
3. Patients learn readily and develop greater confidence because of the ease with which they learn to place and use the diaphragm.
4. Affords patient protection by locking in spermicidal lubricant and delivering it directly under and next to the os uteri.
5. Folds behind pubic bone with suction-like action forming an effective barrier.
6. Simple to remove.

When compressed, diaphragm forms into semi-curve or half-moon shape (Fig. 1) permitting it to pass easily along floor of the vagina beyond cervix (Fig. 2) without any difficulty. No mechanical inserter or introducer required (see Fig. 2) since the KORO-FLEX will not buckle or butterfly in form.

KORO-FLEX (contouring) Diaphragm acceptable, not only where ordinary coilspring diaphragms are indicated but for Flat rim (Mensinga type as well.

May be used in cases of mild prolapse, cystocele or rectocele.

Suggest the convenient-economical KORO-FLEX COMPACT 60-95 mm Sanitary plastic bag with zipper closure. Diaphragm, tube KOROMEX Jelly (3 oz.) Cream (1 oz. trial size).

Available in all prescription pharmacies. Write for descriptive literature.

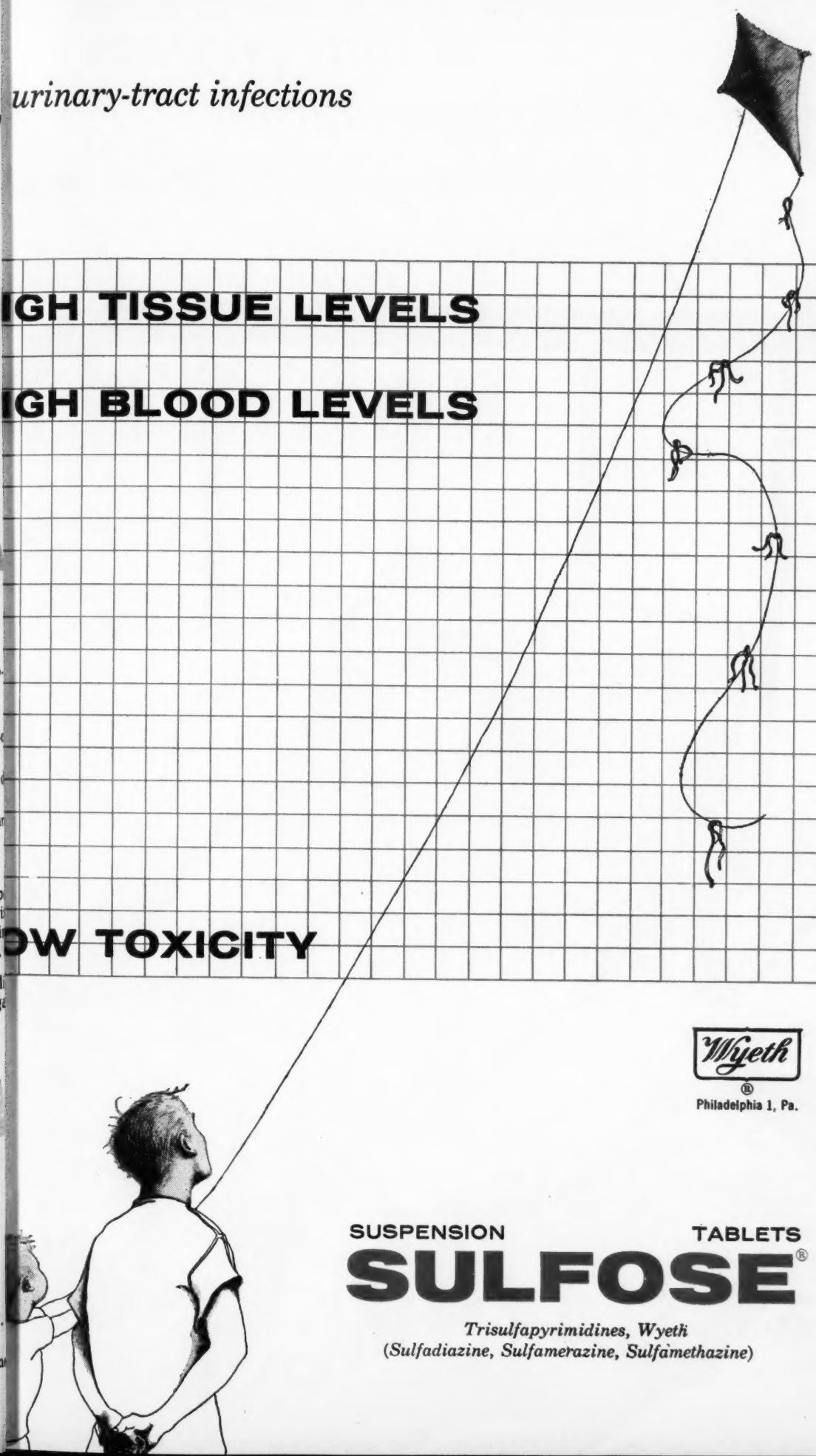
Holland-Rantos Co., Inc. Manufacturers of **KOROMEX** Products, New York 13, N.

urinary-tract infections

IGH TISSUE LEVELS

IGH BLOOD LEVELS

OW TOXICITY



Wyeth®
Philadelphia 1, Pa.

SUSPENSION TABLETS

SULFOSE®

Trisulfapyrimidines, Wyeth
(Sulfadiazine, Sulfamerazine, Sulfamethazine)

in early pregnancy
or hyperemesis gravidarum
in postoperative sta

apid relief of mild or severe nausea and vomiting...

Trilafon*

(pronounced Tril'-a-fon) perphenazine

antiemetic potency

potency increased 5 to 6 times over chlorpromazine[1]

new safeguards in emesis control

relatively high therapeutic index[2]

jaundice notably infrequent in studies to date[1]

virtual freedom from significant hypotension[1,3]

no agranulocytosis reported[1]

skin rashes and nasal congestion uncommon[1,3]

mild insomnia and motor restlessness infrequent[1]

Antiemetic dosage: Average dosage range is 8 to 16 mg. daily in divided doses. Dosage as high as 24 mg. is occasionally necessary.

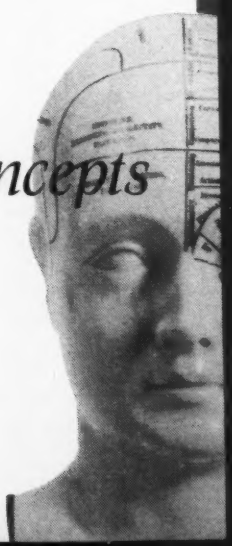
Refer to Schering literature for specific information regarding dosage, side effects, precautions and contraindications.

TRILAFON Tablets: 2, 4 and 8 mg., bottles of 50 and 500.

(1) Compilation of investigative studies, Schering Corporation.
(2) Department of Pharmacology, Schering Corporation.
(3) Ayd, F. J., Jr.: J. Am. Geriatrics Soc. 5:92, 1957.

*T.M. TR-J-957

outmoding older concepts



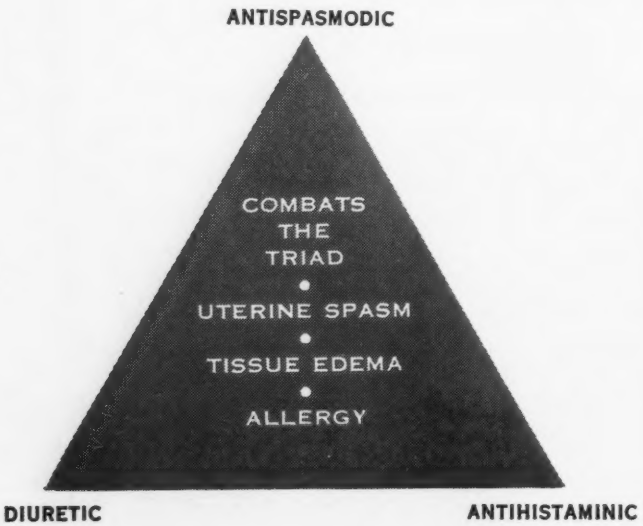
Schering

Announcing

FOR DYSMENORRHEA and PREMENSTRUAL TENSION-DYSMENORRHEA SYNDROME

...a new physiologic corrective contains no analgesic drug

Trilute



Trilute contains

TROCINATE, a clinically prove safe spasmolytic, especially p tent, in pharmacologic studie in relieving spasm of the uter (J. Pharm. Exp. Ther. 89:131

THEOPHYLLINE, a diuretic combat fluid retention and ute ine tissue edema, importa etiologically in the premenstru tension-dysmenorrhea syndrom

PYRILAMINE MALEATE, an an histaminic to combat any allery factor.

IN EACH PINK AND GRAY CAPSU TROCINATE 100 MGMS., THEOPHYLL 100 MGMS., PYRILAMINE MALEATE MGMS.

IN BOTTLES OF 25 AND 100 CAPSU

Directions: One capsule after e meal and at bedtime, beginning 4 d before onset of menstruation, continuing through first day of f

Wm. P. Poythress *& Co., Inc.*

ETHICAL PHARMACEUTICALS • RICHMOND 17, VIRG

when corticosteroids are indicated...

prescribe

PARACORT*

PREDNISONE, PARKE-DAVIS

or

PARACORTOL*

PREDNISOLONE, PARKE-DAVIS

three to five times the activity of
cortisone or hydrocortisone

supplied: PARACORT and PARACORTOL are available as 5 mg. and 2.5 mg. scored tablets; bottles of 30 and 100.

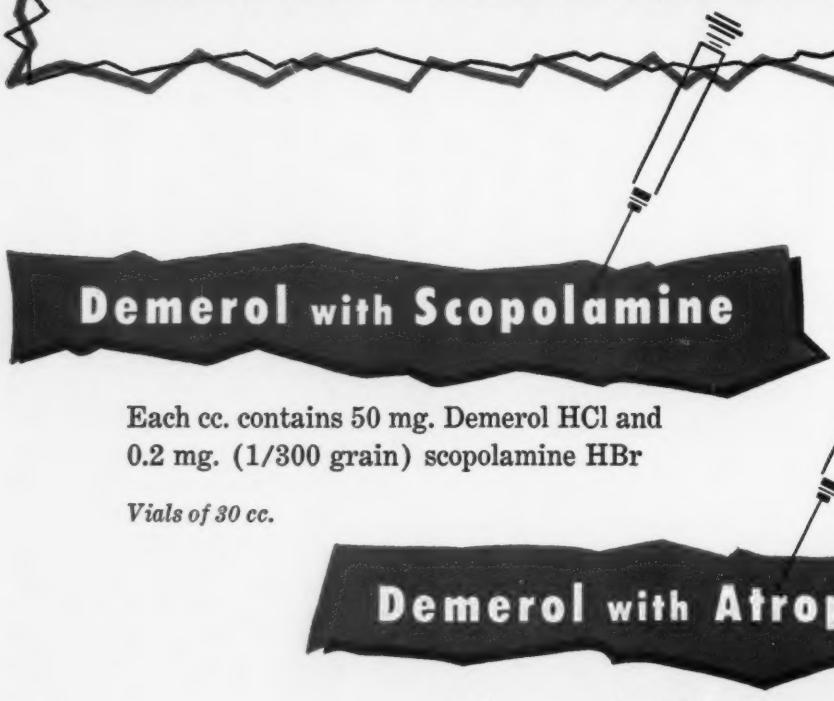
PARKE-DAVIS

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

*TRADE MARK

For Your Convenience

2 NEW Parenteral DEMEROL® COMBINATIONS



Demerol with Scopolamine

Each cc. contains 50 mg. Demerol HCl and
0.2 mg. (1/300 grain) scopolamine HBr

Vials of 30 cc.

Demerol with Atropine

Each cc. contains 50 mg. Demerol HCl and
0.2 mg. (1/300 grain) atropine sulfate

Ampuls of 2 cc., boxes of 25

Subject to regulations of the Federal Bureau of Narcotics.

Winthrop LABORATORIES
NEW YORK 18, N. Y.

Demerol (brand of meperidine), trademark reg. U.S. Pat. Off.

diagnosis
without
delay

Salpix®
contrast medium

in hysterosalpingography
for detecting uterine
and tubal abnormalities

Ortho Pharmaceutical Corporation
RARITAN, NEW JERSEY

Ortho

NOW—the unequalled advantages of K_1—orally

Tablets

MEPHYTON®

(VITAMIN K_1, MERCK)

". . . vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] "Vitamin K_1 appears to be equally effective by the oral or intravenous route."[2] Beneficial effects are apparent in 6 to 10 hours following oral use.

Supplied: Oral MEPHYTON—tablets of 5 mg. of vitamin K_1, in bottles of 100. Emulsion of MEPHYTON—in boxes of six 1-cc. ampuls, 50 mg. of K_1 per cc.

References: 1. Gamble, J.R., et al. Arch. Int. Med. **95**:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. **42**:805, 1953.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC. PHILADELPHIA 1, PA.

An established systemic hemostat

Adrenosem®
SALICYLATE*
(Brand of carbazochrome salicylate)

effective in virtually every operative procedure

The reports of numerous investigators have established the effectiveness of Adrenosem Salicylate in the control of bleeding. It has been used prophylactically and therapeutically in virtually every operative procedure. Following are some of the procedures and conditions where its usefulness has been demonstrated:

Tonsillectomy, adenoidectomy and nasopharynx surgery
Prostatic, bladder and transurethral surgery
Excessive postpartum bleeding and uterine bleeding
Thoracic surgery
Plastic surgery
Gastrointestinal bleeding

ALSO:
Idiopathic purpura
Epistaxis
Retinal hemorrhage
Hematuria
Hemoptysis
Familial telangiectasia
Pulmonary bleeding
Metrorrhagia and menorrhagia

*U.S. Pat. 2581850; 2506294

THE S. E. MASSENGILL COMPANY
Bristol, Tennessee
New York • Kansas City • San Francisco

One of the many uses of **Adrenosem** SALICYLATE

Adrenosem Salicylate is useful in every operative procedure where bleeding and oozing are problems. This hemostatic agent controls blood loss by maintaining normal capillary permeability and by promoting the retraction of severed capillary ends.

One clinician states: "At the recommended dosage levels there are no contraindications. Patients treated for more than two years show no toxic effects attributable to the drug."[1]

Adrenosem Salicylate is supplied in

Ampuls
Tablets
and as a Syrup

1. Riddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, Oral Surg., Oral Med., Oral Path. 6:817 (June, 1955).

Vaginal hysterectomy.
Without Adrenosem. Note bloody field.

Vaginal hysterectomy.
With Adrenosem. Note dry field.

Write for comprehensive illustrated brochure describing the action and uses of Adrenosem Salicylate

THE S. E. MASSENGILL COMPA
Bristol, Tennessee
New York · Kansas City · San Fran

A brighter "Good morning, doctor!"

No complaints about

* post-episiotomy,
* tender hemorrhoids,
* or fissured nipples when you prescribe

Americaine® Topical Anesthetic

Americaine relieves surface discomfort quickly, sustains relief up to six hours with a single application—because only Americaine contains 20% dissolved benzocaine.

What about sensitivities? None reported in over 11,800 published clinical cases[1]...negligible incidence in 10 years' steadily growing use.

Americaine Aerosol

For quick spray application. Available in 3 oz. prescription size, and 5.5 oz. and 11 oz. dispensers.

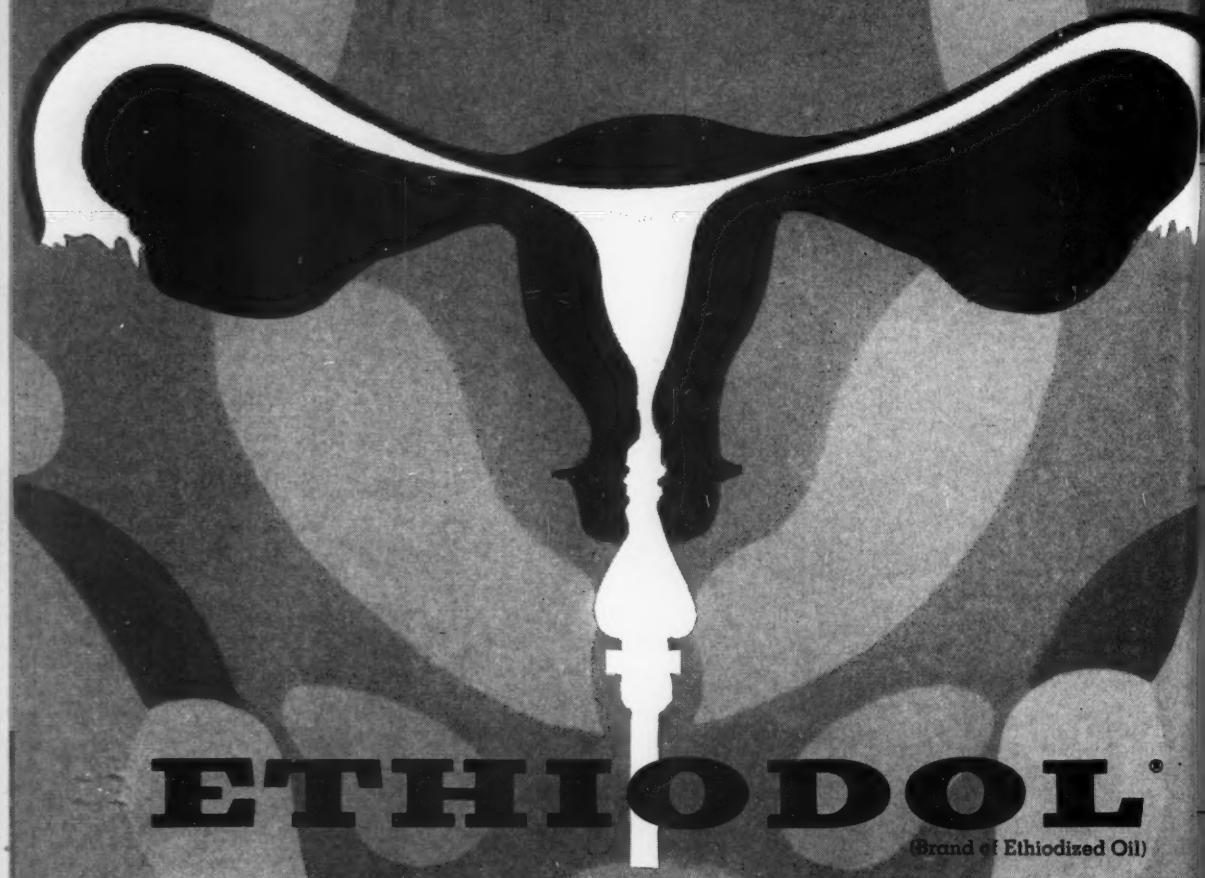
Americaine Ointment

For simple manual application. Available in 1 oz. tube w/applicator.

1. References on request.

ARNAR-STONE LABORATORIES, INC., *Mount Prospect, Ill.*

the advantages you want in hysterosalpingography



ETHIODOL®

(Brand of Ethiodized Oil)

LIPIODOL® diagnostic with free-flowing viscosity

low viscosity for easier administration and free passage through narrow or strictured tubes or openings.

excellent radiopacity provides films as clear as with LIPIODOL for dependable diagnosis.

optimal absorption—completely absorbed usually within 45 days. Permits 24-hour film.

minimal patient discomfort—painless on contact with peritoneum. Bland, nontoxic and nonirritating.

ETHIODOL, brand of ethiodized oil, is the ethyl ester of the iodinated fatty acid of poppyseed oil, containing 37% iodine. Available in 10-cc. ampules, boxes of two. A development of Guerbet Laboratories.

Literature available upon request.

FOUGERA **E. FOUGERA & COMPANY, INC.** • 75 Varick Street, New York 13, N. Y.

31054

during labor...

during delivery...

following delivery...

"THORAZINE* reduces the tendency to vomit . . . and gives the patient almost a detached attitude toward her hospital environment and to labor." –Bonello, F.J.: Internat. Rec. Med. & Gen. Pract. Clin. *169*:197 (April) 1956.

Based on his use of 'Thorazine' during active labor in 110 cases, Bonello finds a double benefit in its administration:

1. Reduced anxiety and apprehension. "The patient becomes placid in her outlook . . . continues to have labor pains regularly, but is almost somnolent between pains . . ."

2. Less danger of aspiration. By substantially reducing the incidence of vomiting, 'Thorazine' improves the patient's safety during anesthesia. No cases of postpartum pneumonia due to aspiration were noted.

Available: Ampuls, Tablets, Syrup (as the hydrochloride), and Suppositories (as the base).

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

Safety First in control of Nausea of Pregnancy

The first thought of every physician during the prenatal period is the safety of the patient.

The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
2. EMETROL has been shown to be effective in nausea and vomiting in controlled clinical studies.[1-3]
3. EMETROL is so palatable that most patients will take it readily.
4. EMETROL works quickly, often bringing relief with the first dose.

SAFE

EMETROL®

(Phosphorated Carbohydrate Solution)

1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.
2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

Kinney

KINNEY & COMPANY, INC

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A "SENSE OF WELL-BEING" IS A WOMAN'S PRIVILEGE

Every woman who suffers in the menopause deserves "Premarin."

Relief from distressing symptoms is promptly obtained and a "sense of well-being" is an extra benefit of therapy.

"Premarin" presents the complete equine estrogen-complex. Has no odor, imparts no odor. Available as tablets or liquid.

"PREMARIN"®

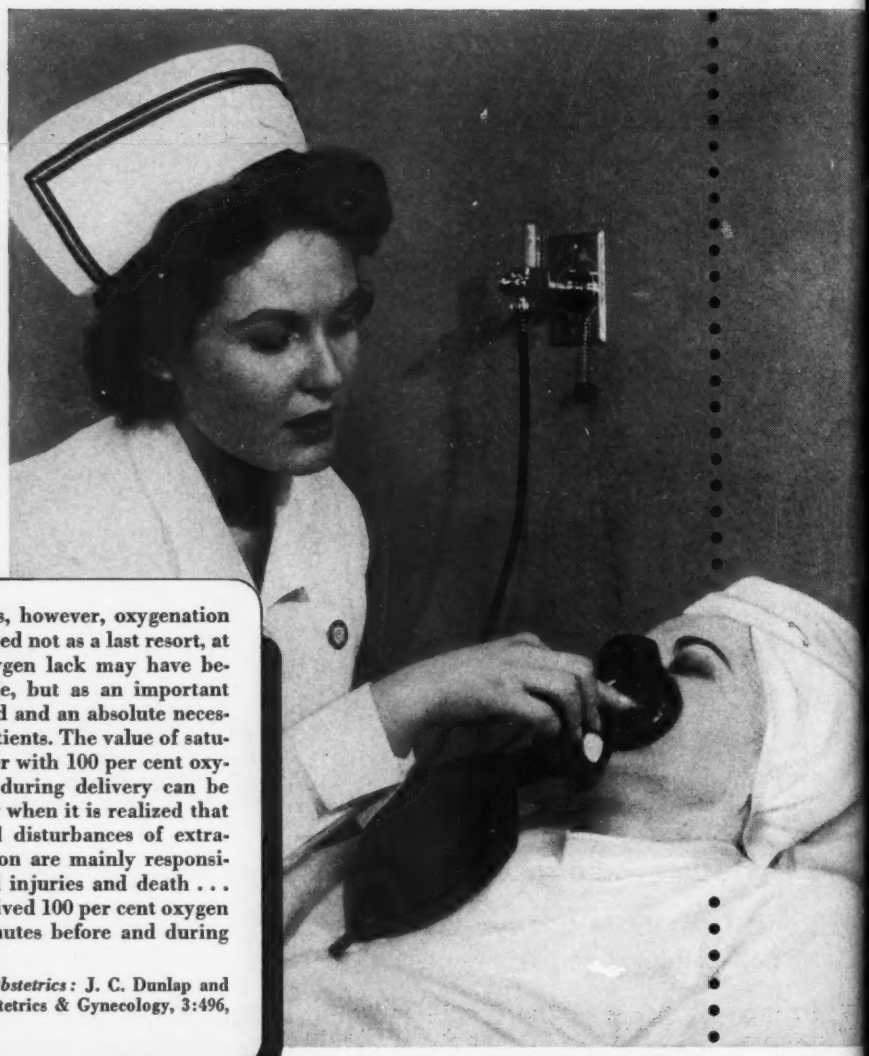
Conjugated estrogens (equine)

in the menopause and the pre- and postmenopausal syndrome

Ayerst LABORATORIES • New York, N. Y. • Montreal, Canada

5644

In obstetrics..... O_2



"... In obstetrics, however, oxygenation should be regarded not as a last resort, at which point oxygen lack may have become irreversible, but as an important routine safeguard and an absolute necessity for many patients. The value of saturating the mother with 100 per cent oxygen before and during delivery can be appreciated only when it is realized that fetal anoxia and disturbances of extrauterine respiration are mainly responsible for perinatal injuries and death ... All patients received 100 per cent oxygen for 20 to 30 minutes before and during delivery."

—*Oxygenation in Obstetrics:* J. C. Dunlap and W. W. Brown; Obstetrics & Gynecology, 3:496, May, 1954.

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TRADE-MARK

producer of highest-purity oxygen for more than 50 years

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Division of Union Carbide Corporation
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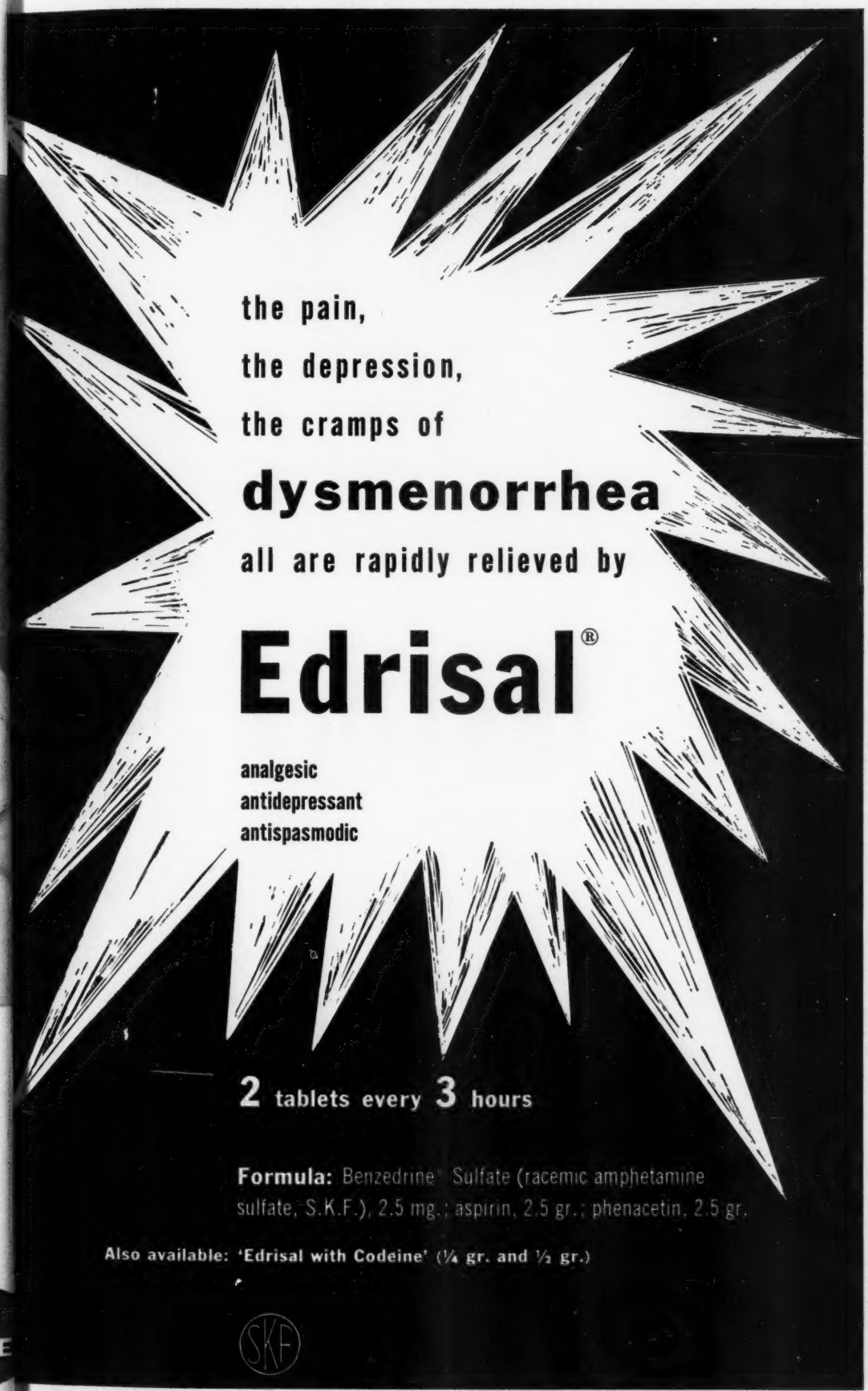
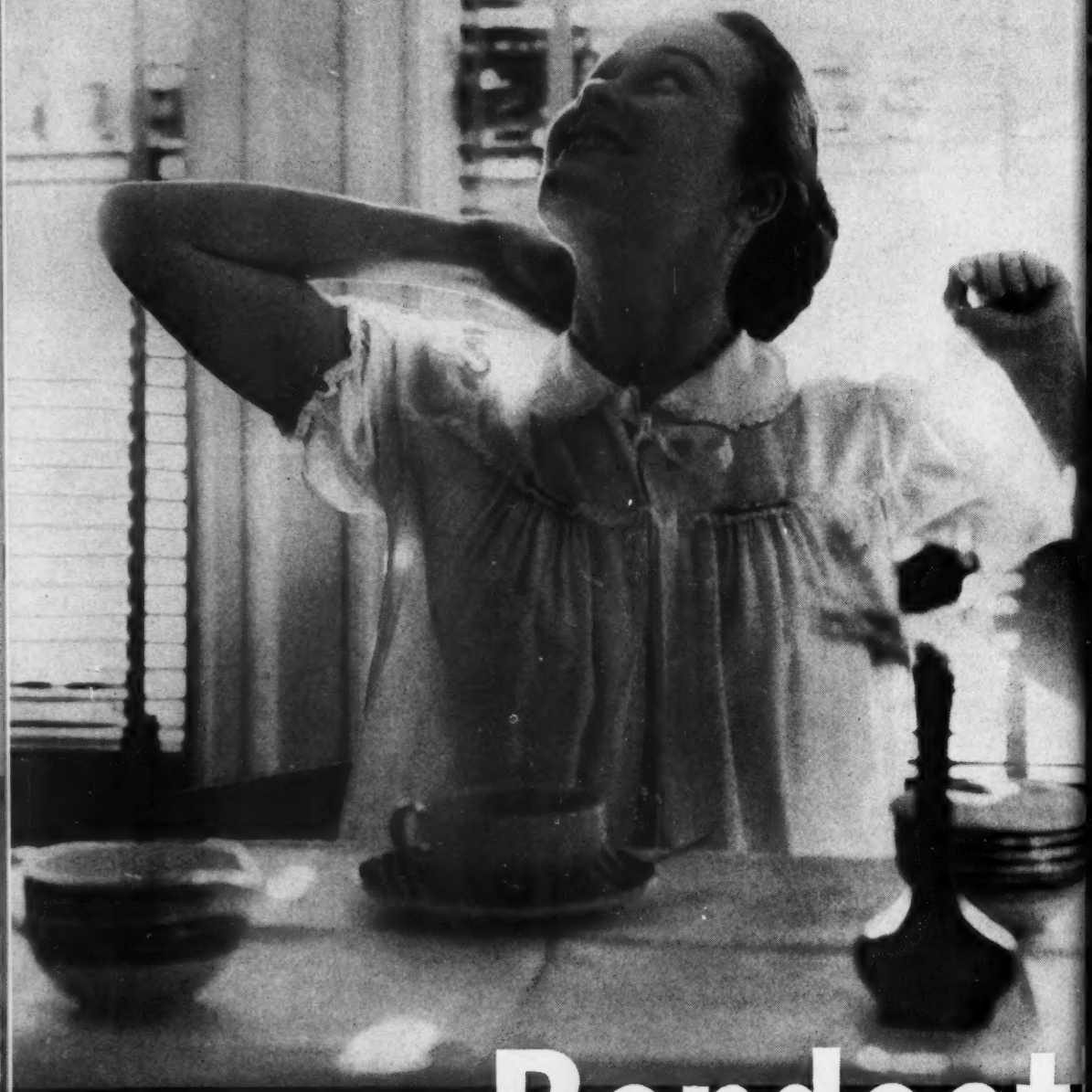
UNION CARBIDE


the pain,
the depression,
the cramps of
dysmenorrhea
all are rapidly relieved by
Edrisal®
analgesic
antidepressant
antispasmodic
2 tablets every 3 hours
Formula: Benzedrine® Sulfate (racemic amphetamine sulfate, S.K.F.), 2.5 mg.; aspirin, 2.5 gr.; phenacetin, 2.5 gr.
Also available: 'Edrisal with Codeine' (¼ gr. and ½ gr.)
SKF

treat her morning sickness... the night b



in 941 cases[1,2] effective in all but 17

Bendect

2 tabs. h. s.

Merrell
SINCE 1828

THE WM. S. MERRELL COMPANY
New York · CINCINNATI · St. Thomas, Ontario
Another Exclusive Product of Original Merrell Research

1. Nulsen, R. O.: Ohio State M. J. 53:665, 1957.
2. Clinical communications, 1956-57.

ostpartum pain

ectively controlled

10 to 12 hours

a single

blet

the first time you can now prescribe ex-
ed action codeine. Donnagesic *Extentabs*
the obstetrician the high level of codeine
gesia he needs[1,2] to help give a restful puer-
um to the 75 per cent of multiparas who
r after-pains.[1]

more than extended codeine analgesia is
ided by Donnagesic. Essential sedation[1,3]
duce pain consciousness and anxiety is also
ided, for Donnagesic contains the balanced
of natural belladonna alkaloids and pheno-
ital of Donnatal®

ther, the phenobarbital augments the potent
gesia provided,[4] while the alkaloids mini-
the possibility of codeine constipation,
ea and vomiting, which occasionally result
codeine administration.

DONNAGESIC	No. 1 (pink)	No. 2 (red)
CODEINE Phosphate	48.6 mg. (¾ gr.)	97.2 mg. (1½ gr.)
Hyoscyamine Sulfate ...	0.3111 mg.	0.3111 mg.
Atropine Sulfate	0.0582 mg.	0.0582 mg.
Hyoscine Hydrobromide..	0.0195 mg.	0.0195 mg.
Phenobarbital	48.6 mg. (¾ gr.)	48.6 mg. (¾ gr.)

Dosage: One or two Donnagesic Extentabs No. 1 or No. 2 every 10 to 12 hours.

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ee, J. B., and Greenhill, J. P.: Principles and Practice of Ob-
rics, Philadelphia, W. B. Saunders Company, 1946; p. 299.
liams, W. J.: Obstetrics, Eastman, N. J. (ed.), New York, Ap-
on-Century-Crofts, Inc., 1950; p. 459.

3. Beck, A. C.: Obstetrical Practice, Baltimore, The Williams and Wilkins Company, 1947; p. 332.
4. Goodman, L. S., and Gilman, A.: The Pharmacologic Basis of Therapeutics, N. Y., The Macmillan Company, 1955; p. 127.

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1. Spiesman, M. G. and Malow, L.: Amer. J. Proctology, June 1956.

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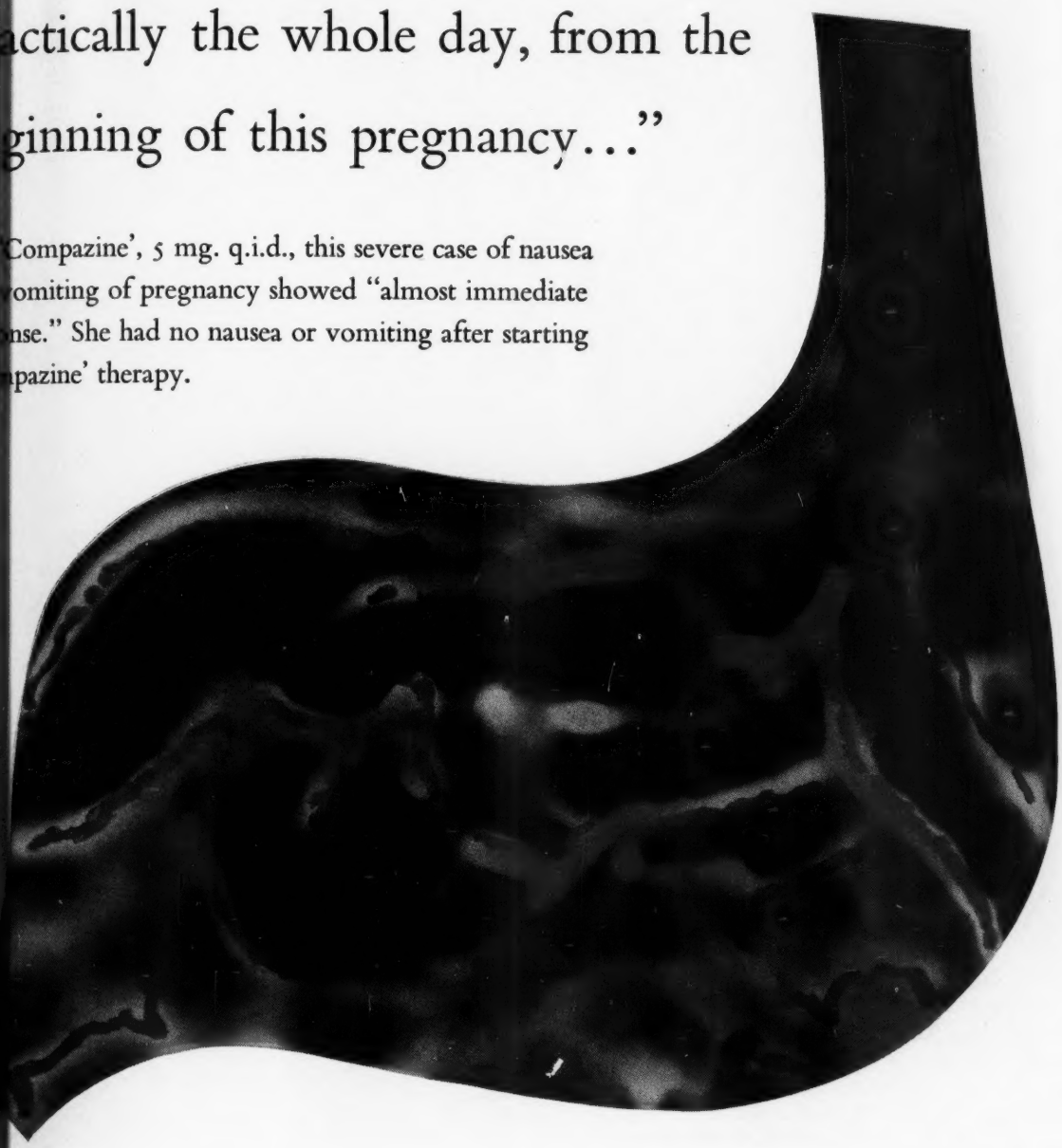

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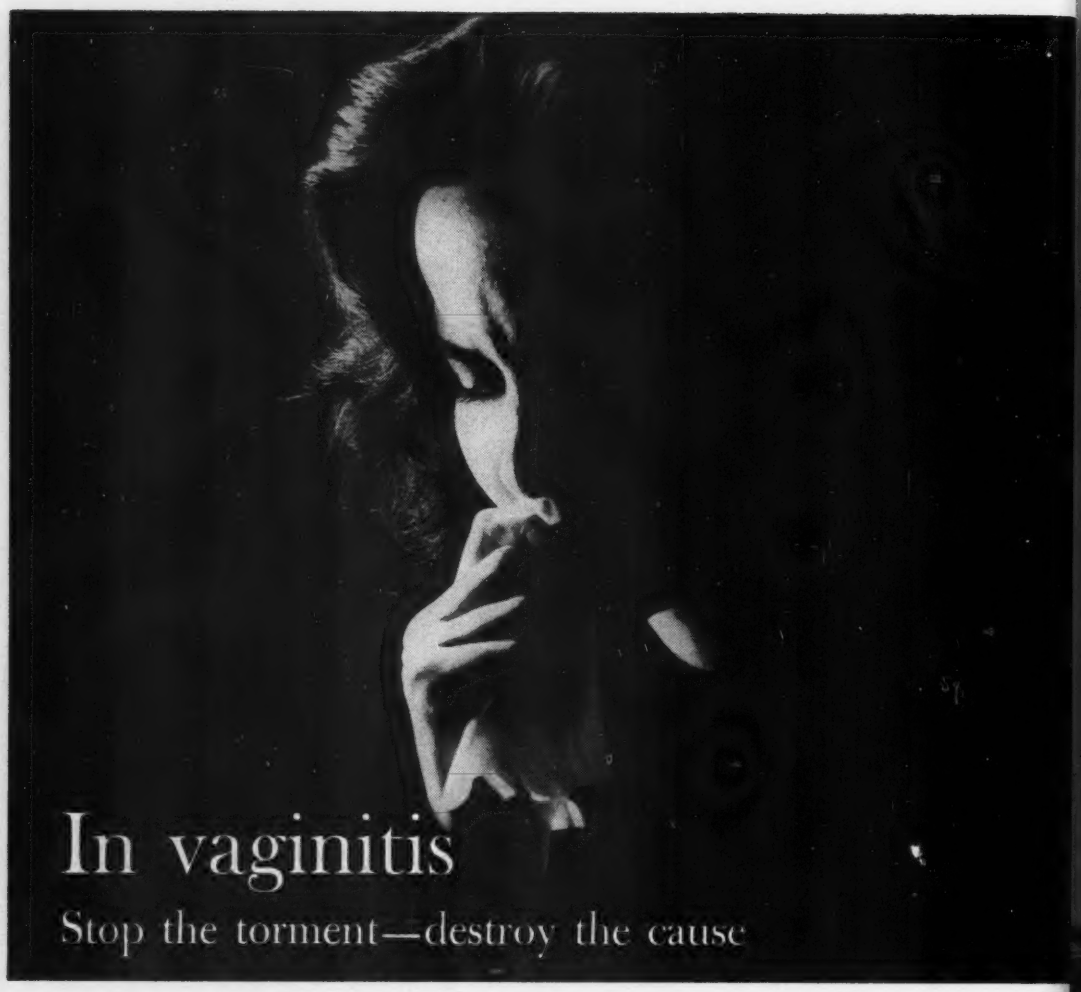

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(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Ho H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1

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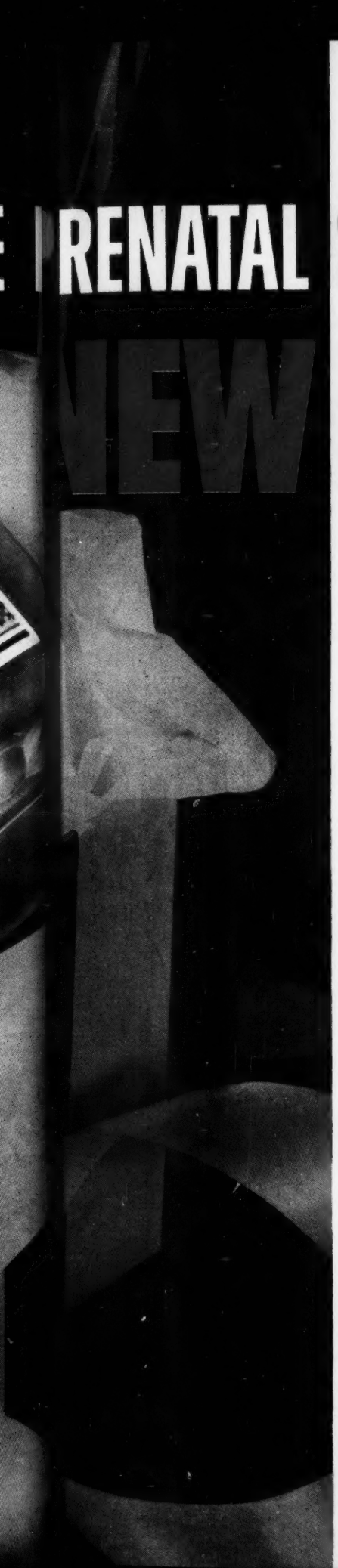

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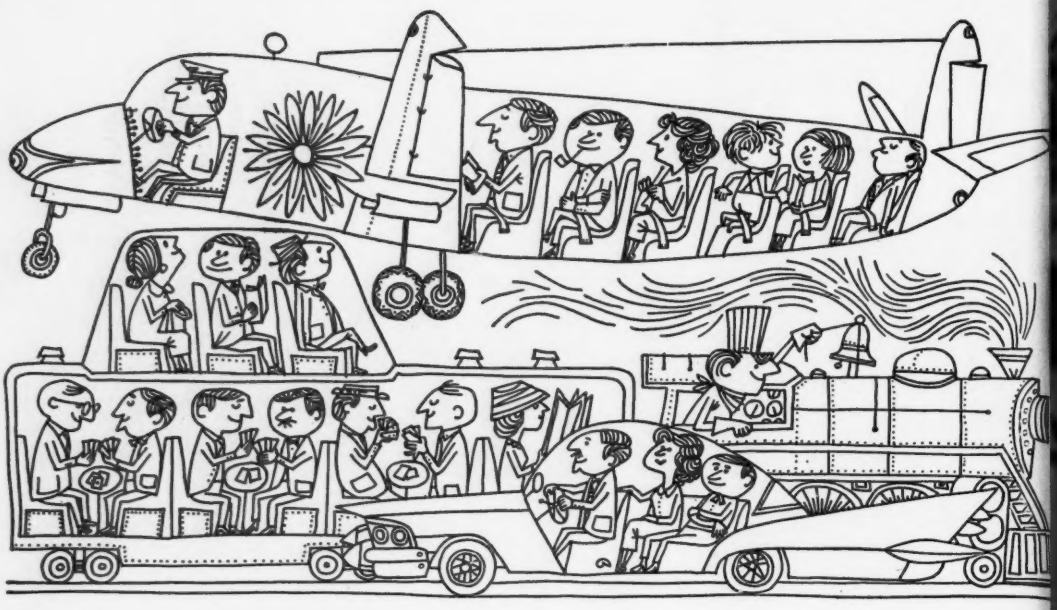

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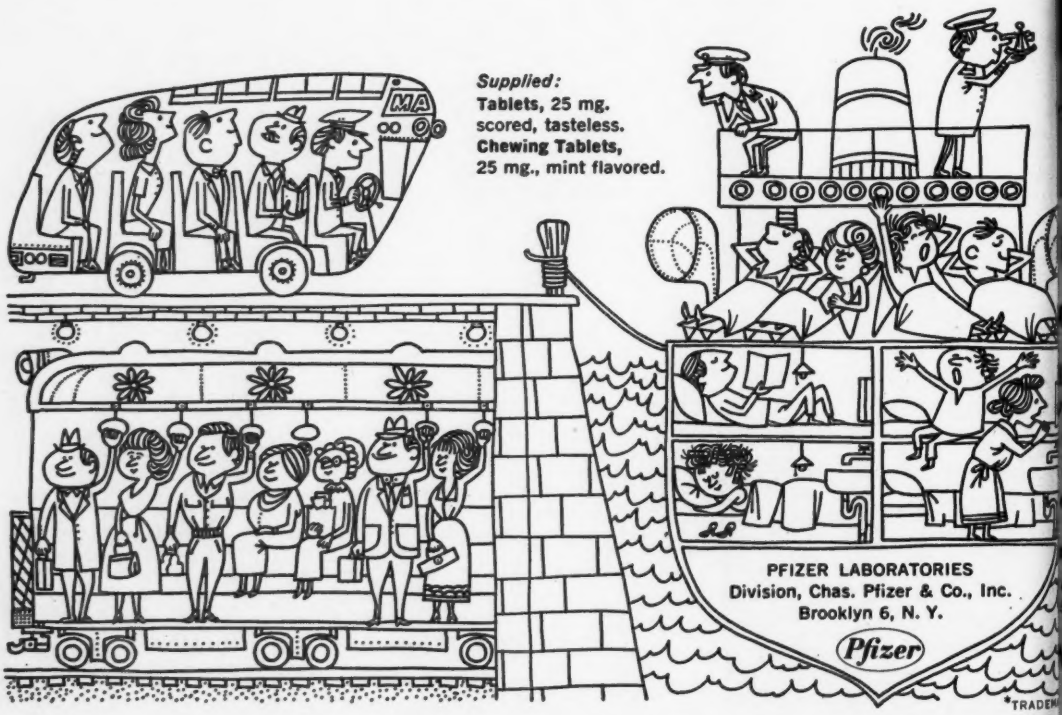

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ar, J.K.B.E., and Devlin, A.J.: Maryland M.J. 5:330 (June) 1956.

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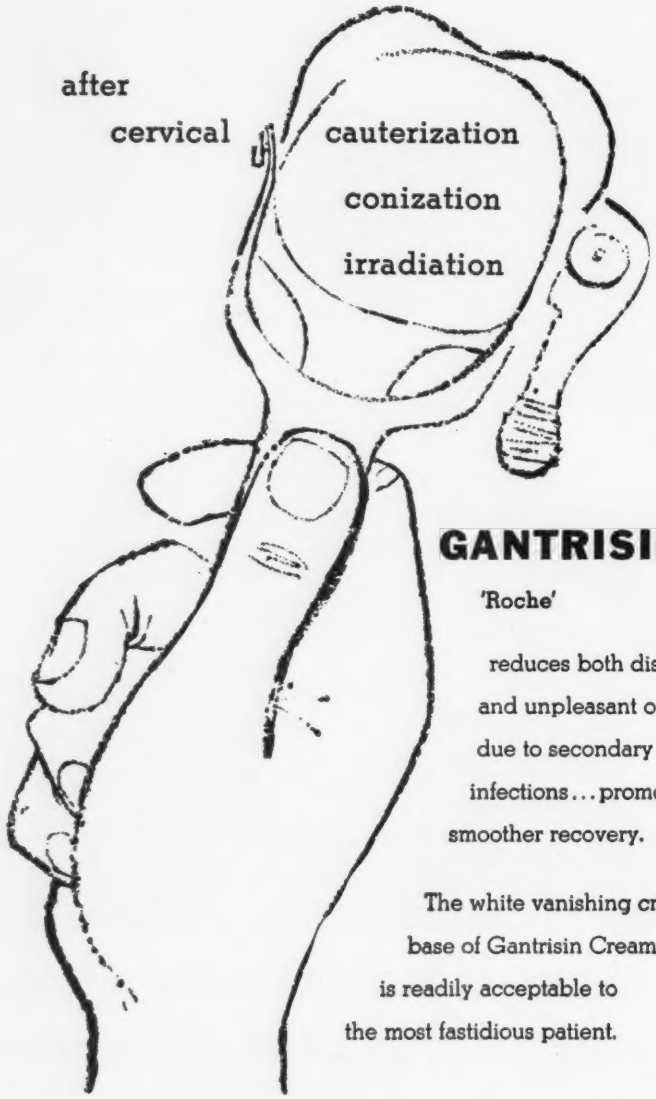

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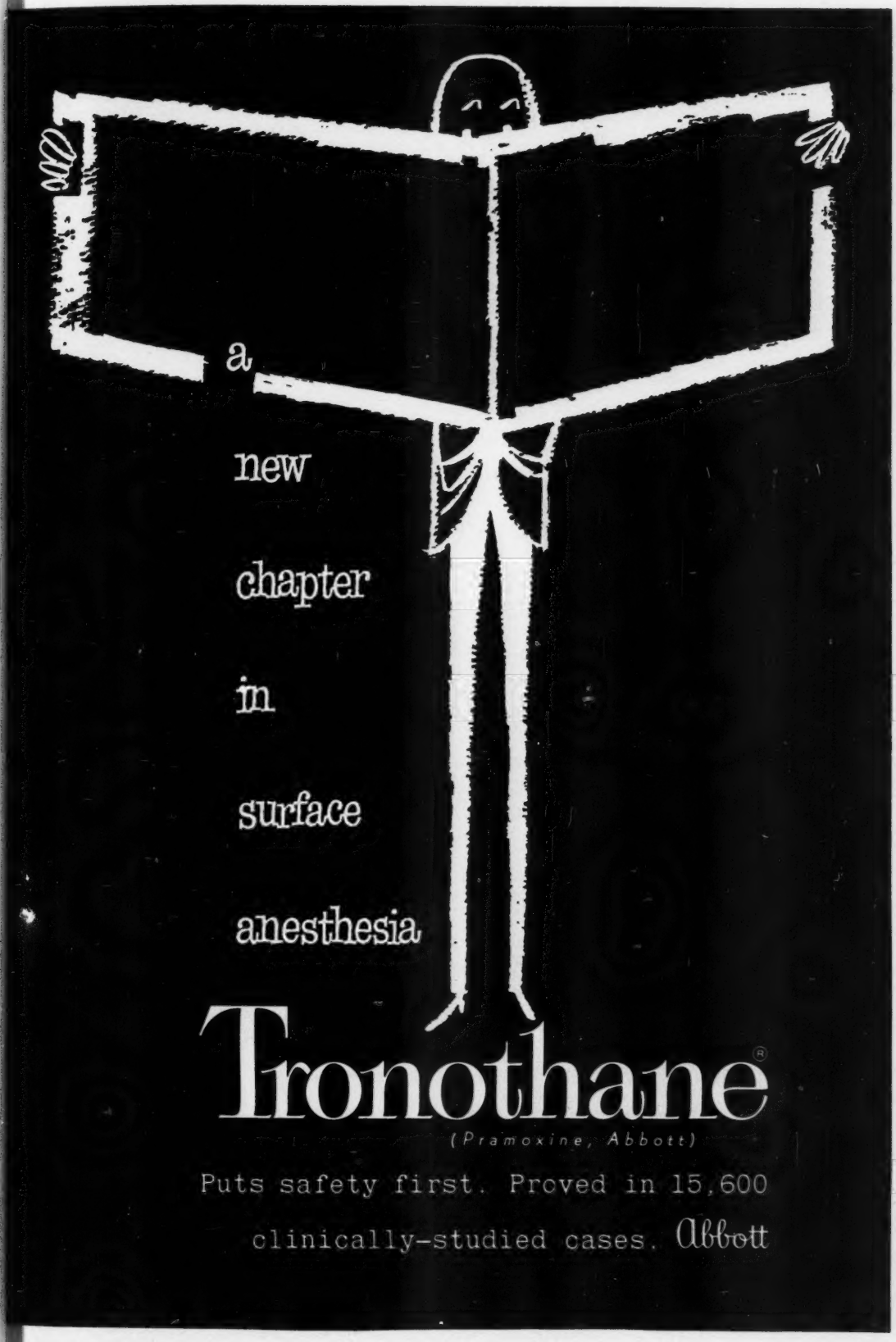
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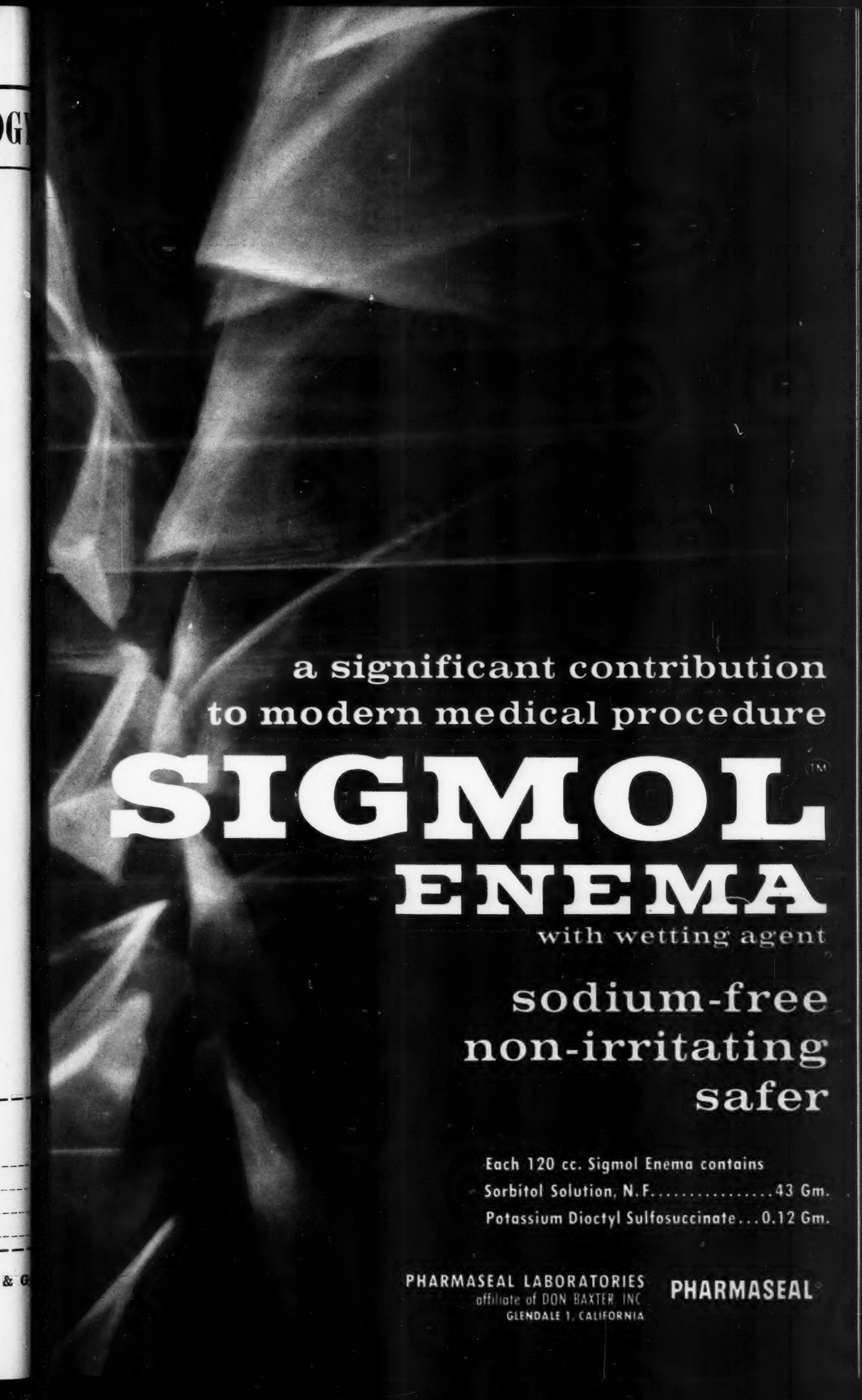
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1. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 2. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657. • 3. Doyle, J. C.: California Med. 71:15 (July) 1949.

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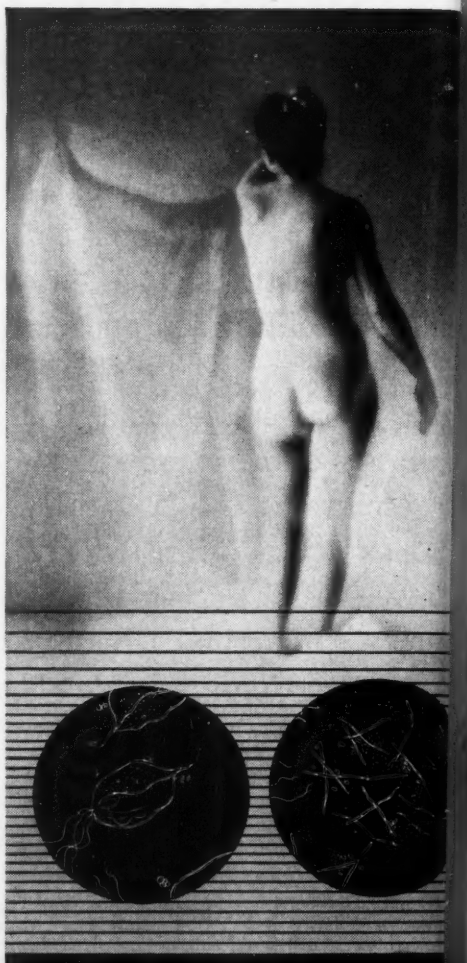
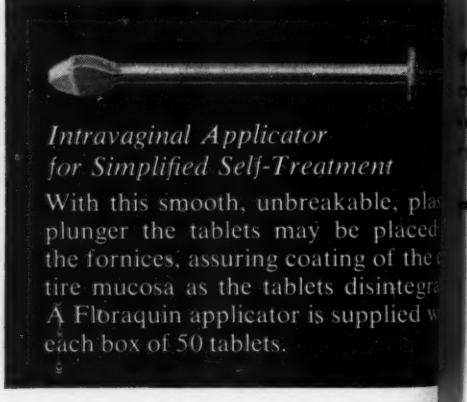
1. Gardner, H. L.; Dampeer, T. K., and Dukes, C. D.: The Prevalence of Vaginitis, A Study in Incidence, Am. J. Obst. and Gynec. *73*:1080 (May) 1957.
2. Williamson, P.: Trichomonad Infestation, M. Times *84*:929 (Sept.) 1956.
3. Lang, W. R.: Recent Advances in Vaginitis, Philadelphia Med. *51*:1494 (June 15) 1956.





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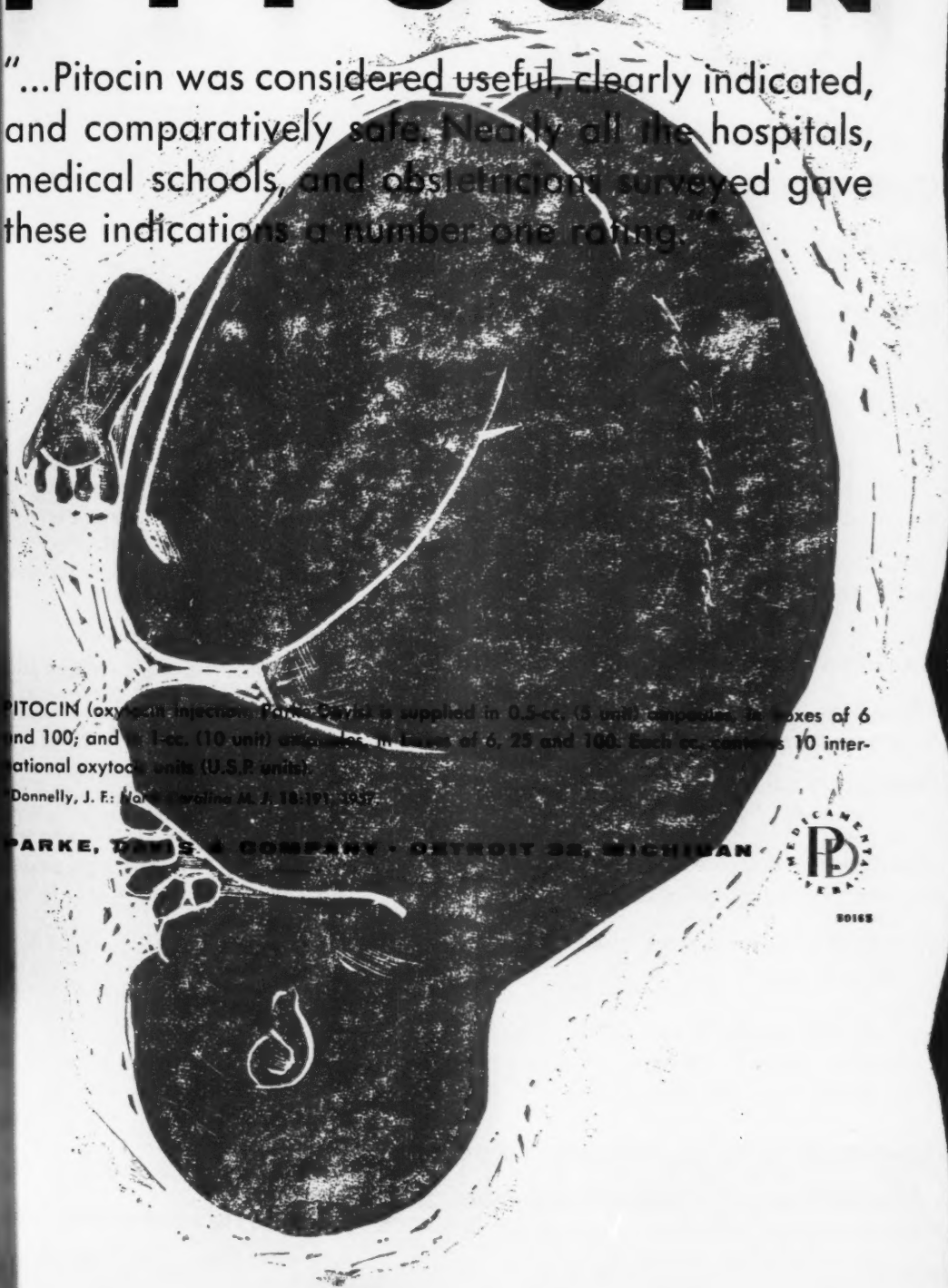

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*Donnelly, J. F.: Modern Medicine, Mt. S. 18:191, 1957.

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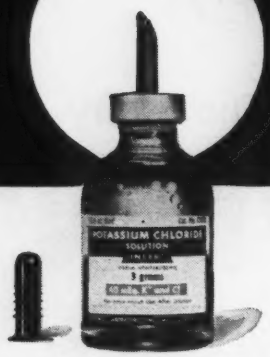

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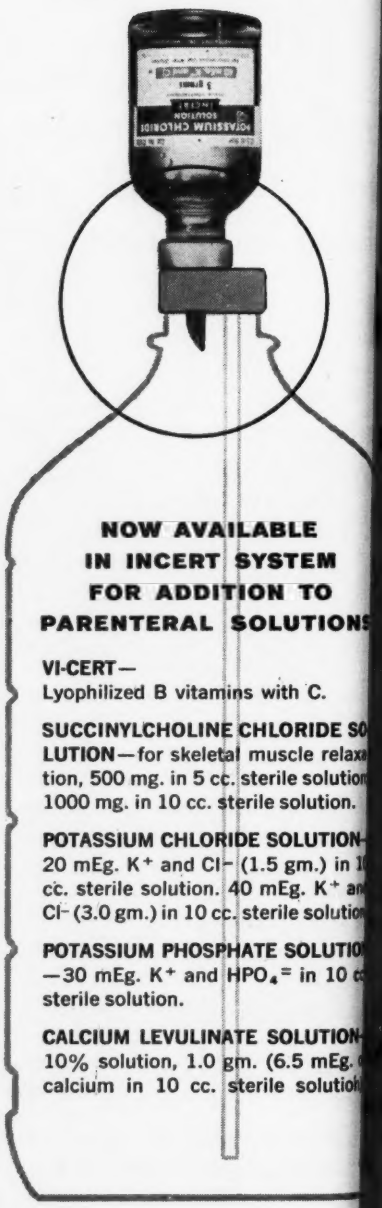

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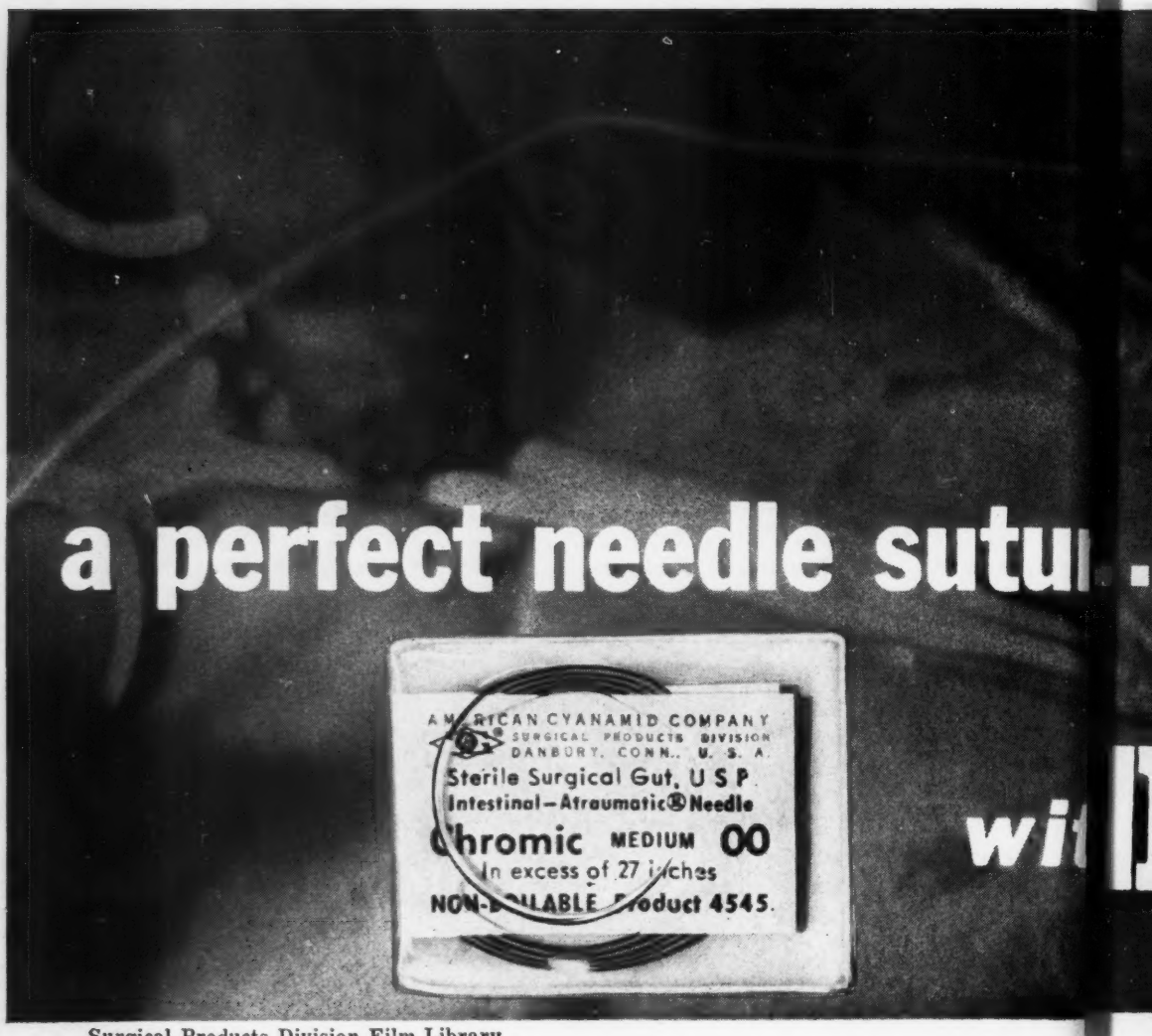

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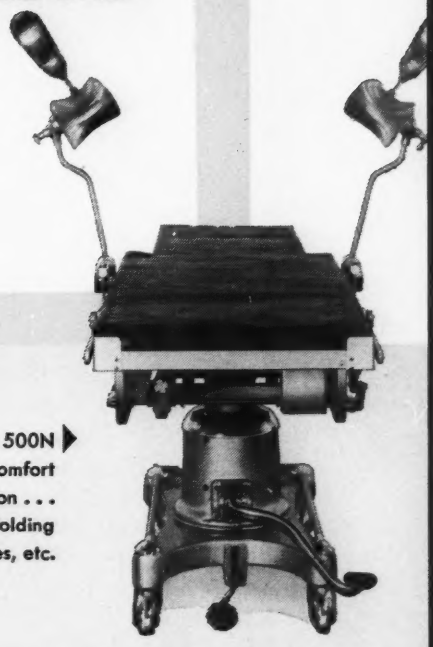

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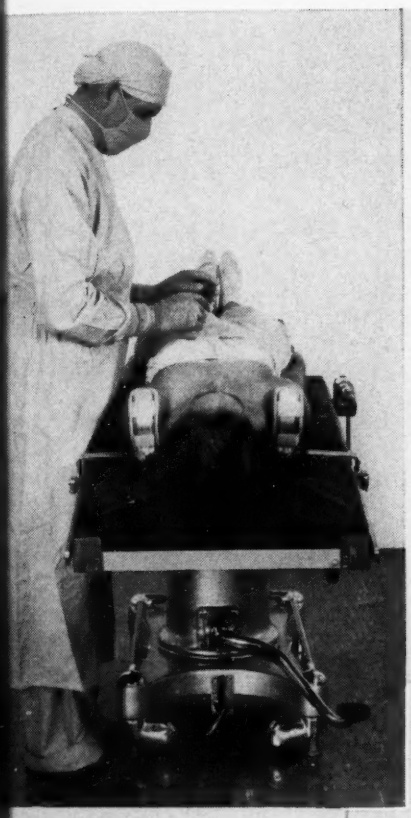

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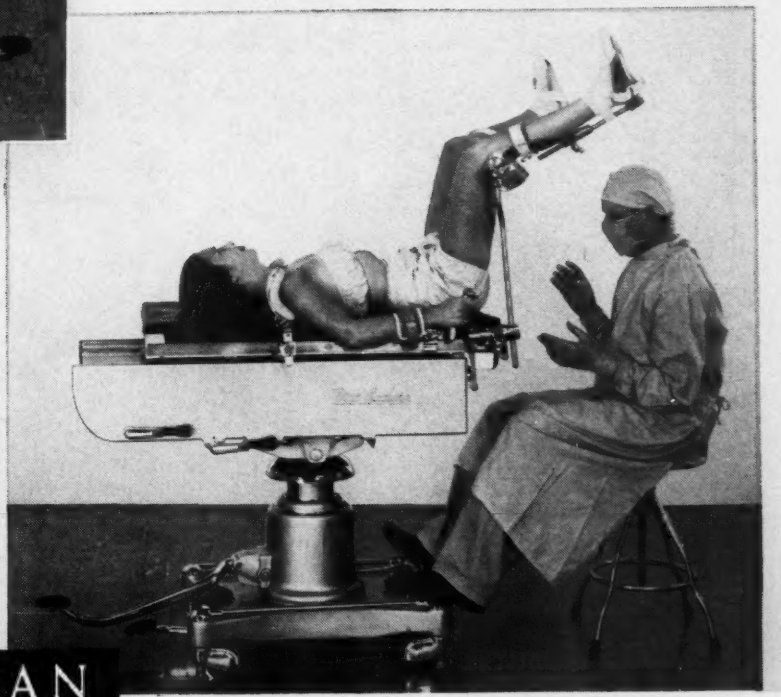

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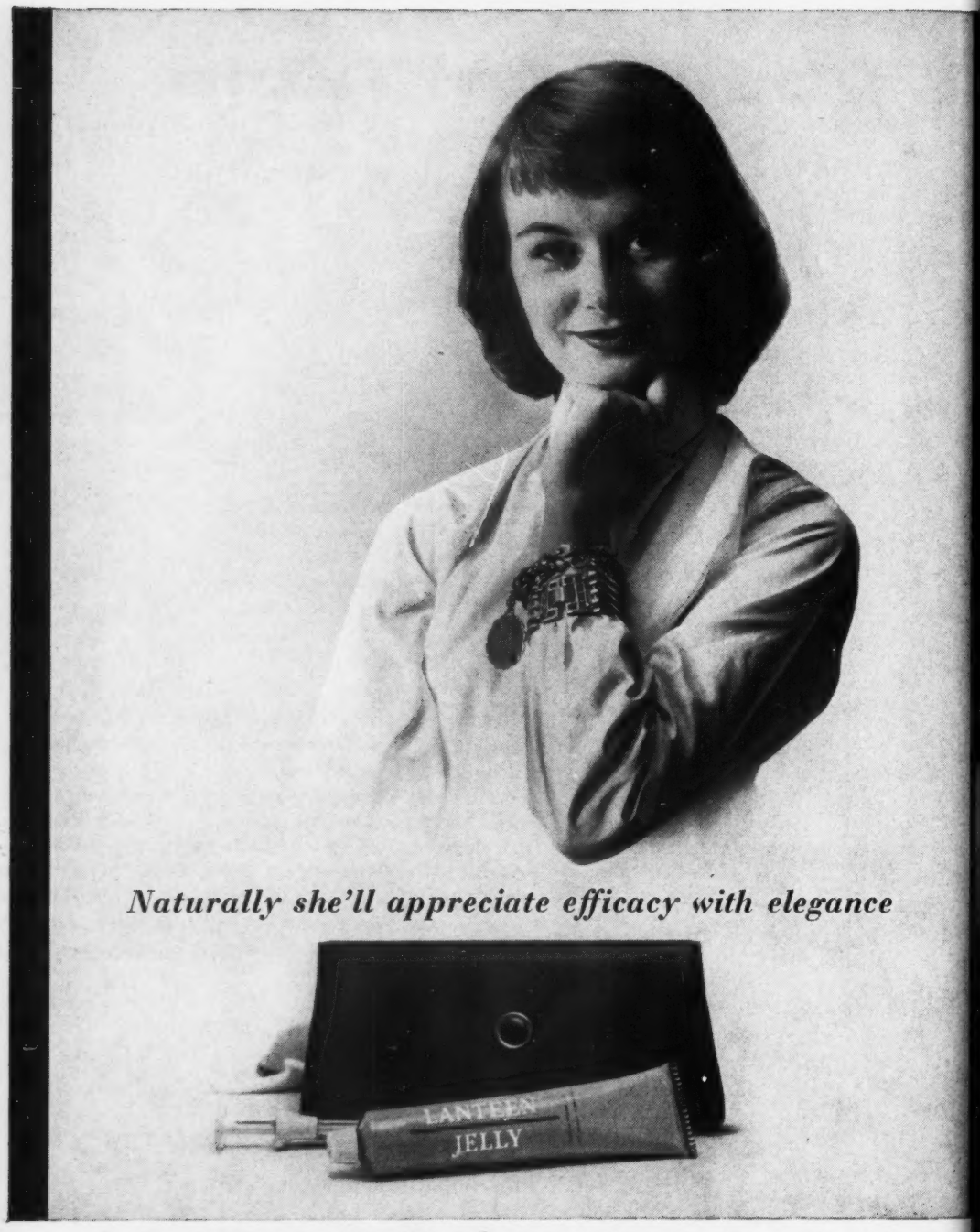

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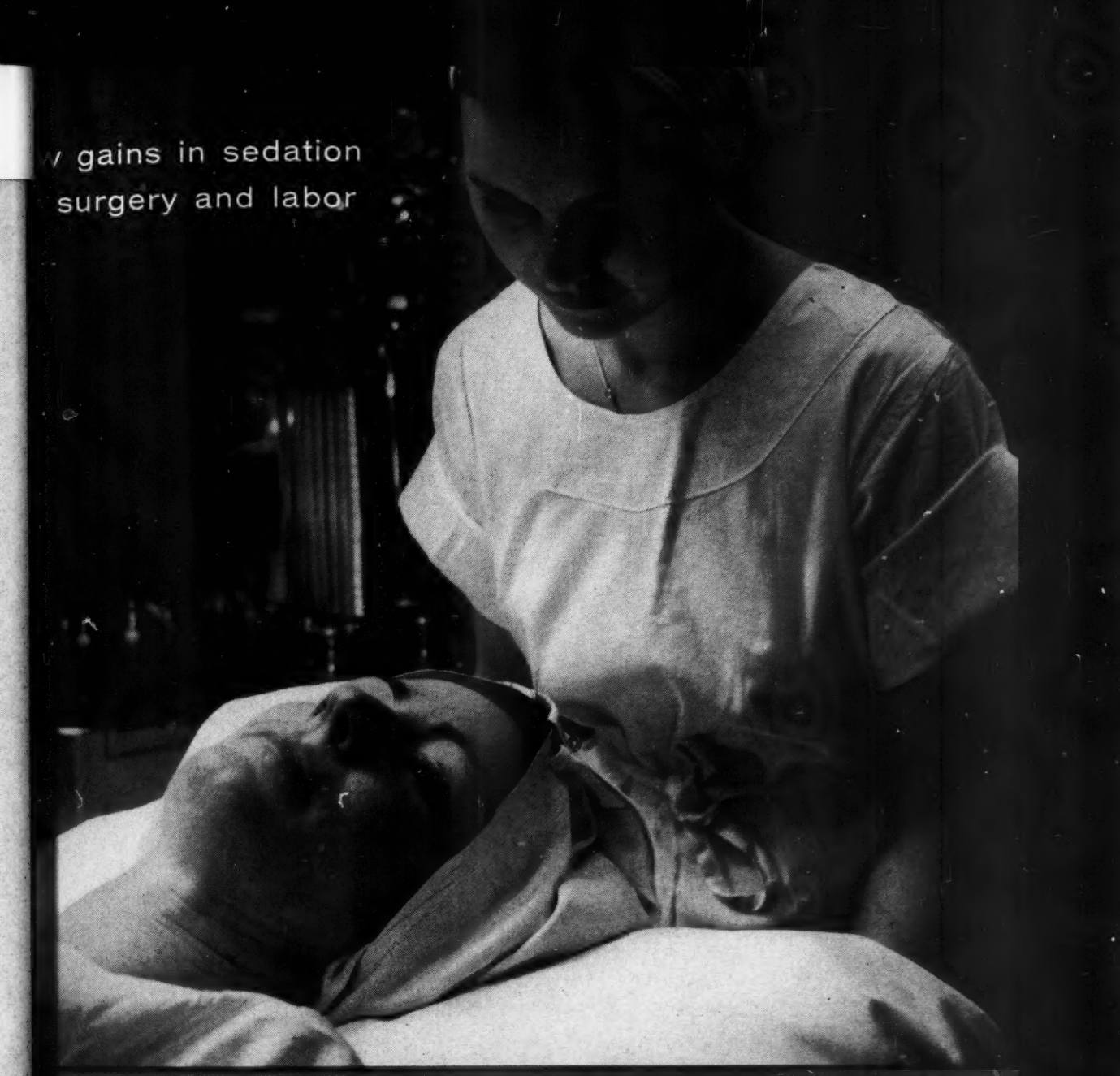

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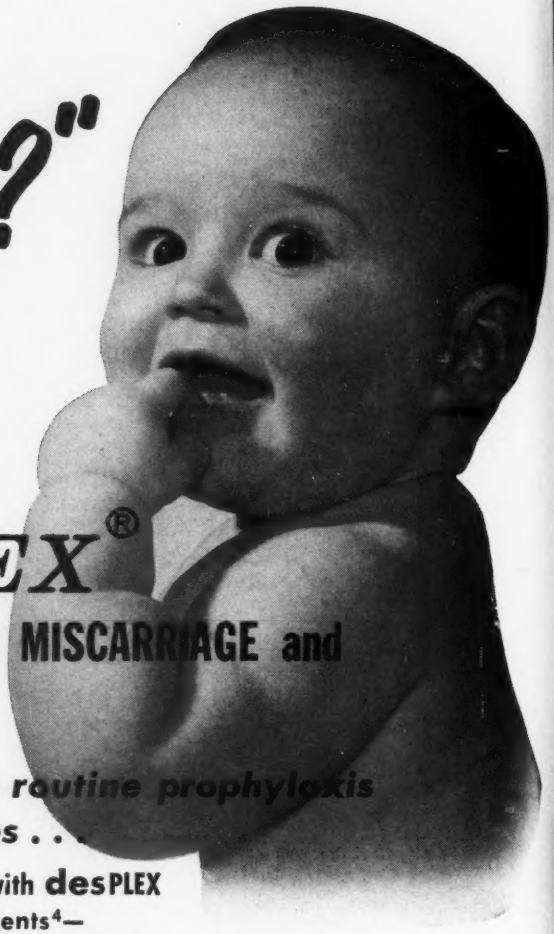

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1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
3. Karnaky, K. J.: South. M. J. 45:1166, 1952.
4. Peña, E. F.: Med. Times 82:921, 1954; Am. J. Surg. 87:95, 1954.
5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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REFERENCES

(1) Chan, Y. T. and Hays, E. E., The American Journal of the Medical Sciences, August 1957; (2) Townsend, E. H., Jr., In Press; (3) Weismiller, F., In Press; (4) Cass, Leo J. and Frederik, W. S., In Press; (5) Curtis, H. C. and Browning, R. H., Ohio State Medical Journal, 42, 500 (1946); (6) Salter, W. T., Textbook of Pharmacology, 84, Wm. B. Saunders, Philadelphia (1952); (7) Hyman, S. and Rosenblum, S. H., Illinois Medical Journal, 104, 257 (1953)

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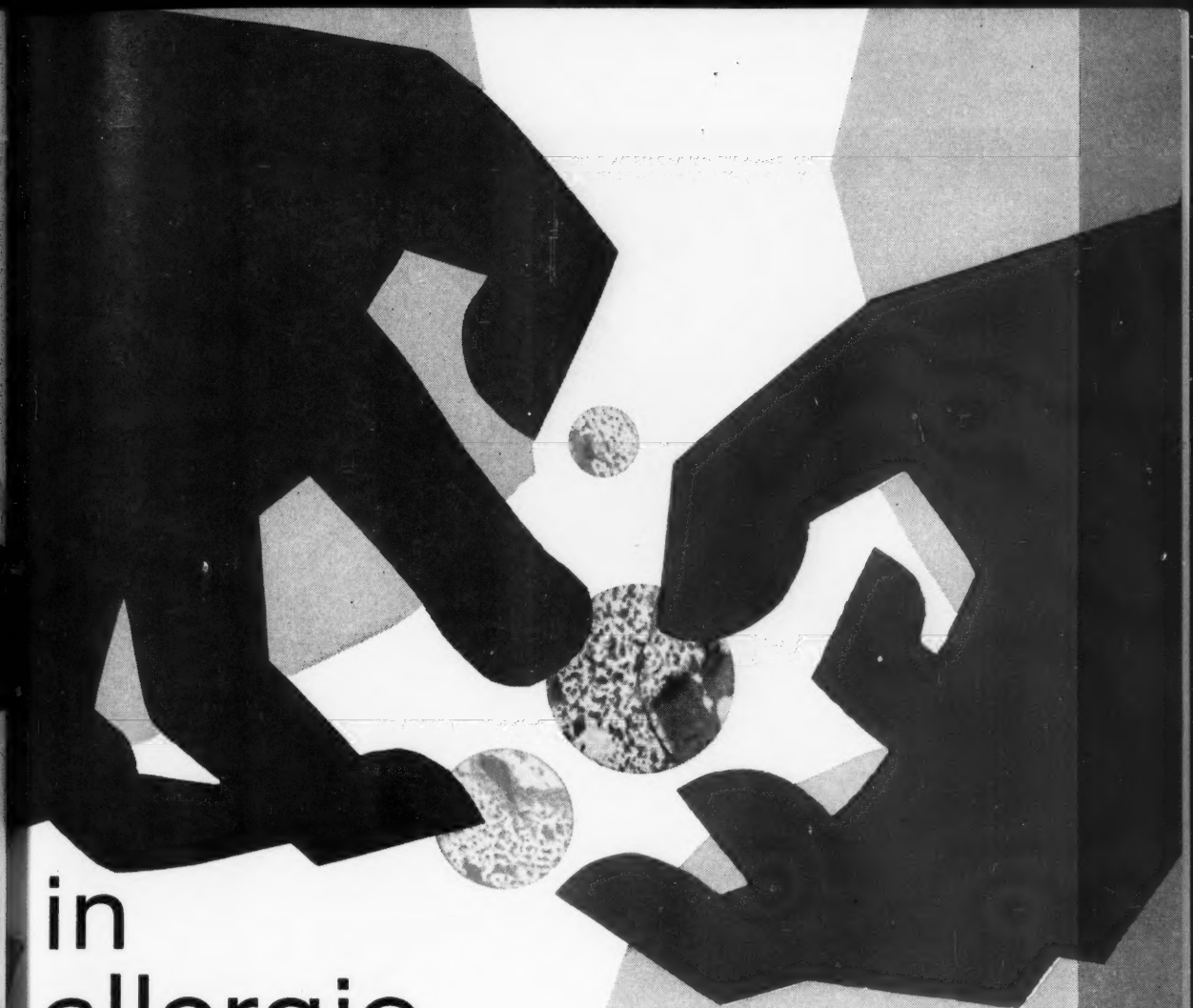

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Vol. 74, No. 3
September, 1957

American Journal of
OBSTETRICS AND GYNECOLOGY

Obstetrics

INTRA-ARTERIAL TRANSFUSION IN OBSTETRICS AND GYNECOLOGY*

CONRAD G. COLLINS, M.D., FREDERICK B. JONES, M.D., WINSTON H. WEESE, M.D.,** JOHN C. THORN, M.D., AND FREDERICK R. BRADEN, M.D., NEW ORLEANS, LA.

(From the Department of Obstetrics and Gynecology, Tulane University School of Medicine, and the Tulane Unit, Charity Hospital of Louisiana at New Orleans)

CHARITY Hospital of New Orleans is the triage point for many neglected and difficult obstetrical and gynecological cases derived from the system of Charity Hospitals in Louisiana and surrounding areas. By reason of this propensity and because of the very large obstetrical services of this hospital, we encounter an inordinate number of acute abdominal catastrophes, usually produced by massive intra-abdominal hemorrhage resulting from ruptured ectopic pregnancies, ruptured uteri, and abdominal pregnancies. We also have large numbers of patients in severe shock due to postpartum hemorrhage, potassium permanganate burns of the vagina, and incomplete abortions.

Over a period of years certain principles have evolved on the Tulane Unit of Charity Hospital in the management of these cases of massive intra-abdominal, uterine, or vaginal hemorrhage resulting in severe shock. One of the most useful and life saving procedures in our hands has been intra-arterial transfusion. One should remember that the patients in whom we utilized intra-arterial transfusions were in profound shock, in extremis from blood loss, and very active treatment was indicated.

*Aided by a grant from the Ex-Resident's and Fellows' Research Fund.

**Instructor in the Department of Obstetrics and Gynecology, Louisiana State University School of Medicine.

Even though intra-arterial transfusion was described by Halsted[1] in 1883 for the treatment of carbon monoxide poisoning, and there have been reports in the literature from time to time regarding intra-arterial transfusion, there has been little done to analyze the problems involved, both physiologically and technically, until recent times.

Veal[2] stressed three important changes that affect the flow of blood to the vascular system as it occurs in shock: (1) reduction in circulating blood volume, (2) fall in blood pressure, and (3) diminution in volume and rate of perfusion to the capillary bed. When the degree of hematogenic hypotension reaches a critical level, which most authorities agree is somewhere around 50 to 60 mm. Hg systolic, often large quantities of blood given intravenously may fail to restore circulatory stability. This happens because of collapse of the capillary bed and any blood administered intravenously would have to pass through the lesser circulation and would tend to cause pooling of blood in the venous system. Kohlstaedt and Page[3] have shown that massive intravenous transfusions at this stage may even cause the right heart to fail.

The effects of hemorrhagic shock on the hearts of intact dogs have been studied by Hackel and Goodale[4] and suggest that the alterations in myocardial carbohydrate metabolism, relative oxygen deficiency, and occasionally subendocardial hemorrhage or necrosis, resulting from decreased coronary artery flow, may predispose to eventual cardiac and circulatory collapse. Salisbury[5] has shown that the efficiency of the right ventricle is directly related to the coronary artery pressure and to aortic root pressure. There is opportunity to increase the efficiency of the right heart in increasing the coronary arterial flow by increasing aortic pressure or arterial reservoir. The influence of pressor agents on incompetence of the right ventricle has been studied by Wolff[6] in successfully treating cor pulmonale caused by pulmonary embolism with arterenol. State[7] confirmed the increase in right ventricular strength produced by increasing arterial pressure augmented by increased coronary artery flow. To obtain forceful cardiac contractions and re-establish perfusion of blood through the peripheral system, the arterial pressure must be raised rapidly. At this stage, intra-arterial transfusion appears best. It has been shown experimentally that blood administered intra-arterially may fill the entire arterial system before an appreciable amount enters a vein. As soon as the aortic pressure is elevated, the intra-aortic resistance is increased and the heart pressure rises and allows a more forceful contraction and propulsion of blood into the aorta. By elevating the intra-arterial pressure, a more adequate perfusion throughout the vascular bed is obtained with increased coronary artery flow, improved myocardial oxygenation and lessened danger of subsequent cardiac failure.

The following facts concerning cardiac and circulatory physiology are pertinent:

1. The flow of blood through the vascular system begins with the pumping action of the heart.

2. For adequate output and to maintain the circulation, the heart must receive sufficient blood to fill its chambers.

3. The cardiac valves must be competent and the heart must build up pressure before ejecting blood into the aorta.

4. Blood volume must be large enough to give resistance during the build-up period.

5. There must be sufficient volume of blood in the arterial system to transmit the force and momentum if adequate perfusion is maintained.

Veal[8] and his workers further established the fact that, in mild grades of hematogenic shock in dogs, either arterial or intravenous transfusions overcame mild degrees of shock. In the moderately severe stages, both methods of transfusion were still effective but results were more rapid with the intra-arterial method and smaller amounts of blood were required. In grave states of shock, the same amount of blood as that withdrawn given intravenously failed to overcome shock, but did succeed when given intra-arterially. Haxton[9] demonstrated the following facts: Dogs which have been exsanguinated to the point of respiratory and cardiac arrest can be revived by intra-arterial but not by intravenous transfusion. Rapid intravenous transfusion hastened death in some. In partially exsanguinated dogs, the quantity of blood transfusion required to restore the blood pressure to normal is only one-half as large if given by the intra-arterial route.

Choo[10] bled dogs into respiratory arrest and showed that after two minutes of arrest 75 per cent revived after intra-arterial transfusion as against 25 per cent revival with intravenous transfusion. After three minutes of arrest 75 per cent recovered with intra-arterial transfusion as contrasted with 15.3 per cent with intravenous transfusion. After 4 minutes' arrest 60 per cent recovered with intra-arterial administration of blood while only 20 per cent recovered if the blood was given by the intravenous route. Bingham[11] agreed in general with these basic experiments.

Robertson[12] showed that when over 50 per cent of the circulating blood volume was removed, intra-arterial transfusion produced adequate results four times as rapidly as did intravenous transfusion. Kohlstaedt and Page[3] agreed.

All investigators, however, do not agree. Kohlstaedt and Page again measured coronary blood flow and arterial pressure using both procedures and found no difference in response. Maloney[13] measured cardiac output and mean arterial pressure and found no difference in either route. Case[14] corroborated Maloney's findings. Artz,[15] in Korea, in 13 cases of severely wounded men, found no difference. His perfusion rate of 88 c.c. per minute, we feel, is too slow from which to draw comparison.

From the work of many investigators and from our clinical experiences we find the following advantages of intra-arterial transfusion:

1. Rapid transfusion can be given to patients with collapsed peripheral vessels.

2. There is a rapid perfusion of blood through the coronary, cerebral, and renal vascular systems.

3. A rapid sustained increase in blood pressure is obtained.

4. It is useful in patients in shock who have failed to respond to intravenous blood.

5. Relatively smaller quantities administered intra-arterially give better results than larger amounts administered intravenously.

6. There is less danger of overloading the right heart and pulmonary circulation.

7. Initially, the blood does not have to pass through the lesser circulation. It is often effective with respiratory and cardiac arrest.

8. Most important in obstetrical and gynecological surgery is that one always has an artery readily available. *This is especially true when severe shock occurs during an abdominal procedure.*

In using intra-arterial transfusion there are some disadvantages that must be kept in mind. The danger of air embolism is paramount. If a peripheral artery is used, it requires surgical isolation, and the danger of ischemic changes distal to the site is present. We do not advocate the use of the radial artery. Gangrene of the hand following its use has been reported by Porter and associates[16] and Yee, Westdahl, and Wilson.[17]

Method

If shock is due to massive intra-abdominal hemorrhage we do not procrastinate about opening the abdomen. Some surgeons will not operate on patients in severe shock and will often waste valuable time trying to expose a peripheral vein, which has collapsed as a result of the blood loss, and pump in large quantities of blood in an attempt to combat shock before operating. The type of patients in whom we have used intra-arterial transfusions were in severe shock from hemorrhage and often in extremis. They usually had only a feeble, extremely rapid peripheral pulse rate, or heart sounds with no obtainable blood pressure. In treating shock from hemorrhage, the bleeding point or points must be ligated.

With the abdomen open, one can stop the bleeding immediately. Also one then has some of the largest arteries in the body available for immediate intra-arterial transfusion. After controlling the bleeding process, we proceed to reflect the lateral parietal peritoneum, exposing the common iliac artery. During the interim, while the operating room is being set up and the abdomen opened, transfusion of blood via the intravenous route is maintained under pressure. Often one can expose the iliac artery before another team can expose a peripheral vein. With the artery exposed, one takes a standard transfusion set, preferably but not necessary sterile, and bends the needle, which is usually a No. 18, to an obtuse angle so it may parallel the lumen of the vessel. The needle is then inserted in a cephalad direction into the vessel. Whole blood transfusion administered intra-arterially may then be initiated, maintaining a pressure considerably above that within the arterial system. This is accomplished by attaching a simple sphygmomanometer bulb and rubber tubing with a Luer-Lok needle attachment onto the needle in the air vent in the bottle containing blood. It is best to have a manometer in the circuit but this is not necessary. The person handling the pump must be reliable and be careful that he does not completely empty the blood from the bottle and pump in air,

causing air embolism. The latter may be fatal. We stop pumping when 100 c.c. of blood is left in the bottle and then clear the system of air before starting another bottle. Less than 500 c.c. of blood given intra-arterially will be sufficient to restore blood pressure and efficient cardiac output in most cases.

Continuous blood pressure determination during intra-arterial transfusion is necessary in order that excessive intra-arterial pressure not be produced. The blood pressure should not be elevated above normal levels.

When the blood pressure has risen, and it usually does so rapidly, one should remove the needle and with gentle pressure stop the bleeding from the puncture site. If it persists, we have had, on occasions, to close the puncture site with a fine silk suture.

Following completion of the intra-arterial transfusion, the adventitia of the artery is perfused with 1 per cent procaine to relieve vasospasm which will be visibly noted within seconds by the dilatation of the artery grossly to normal or slightly above normal size as contrasted with the corresponding vessel on the opposite side.

Lumbar sympathetic blocks may be used postoperatively if signs or symptoms of vasospasm persist. The legs and peripheral pulsations are observed every hour for signs of the latter.

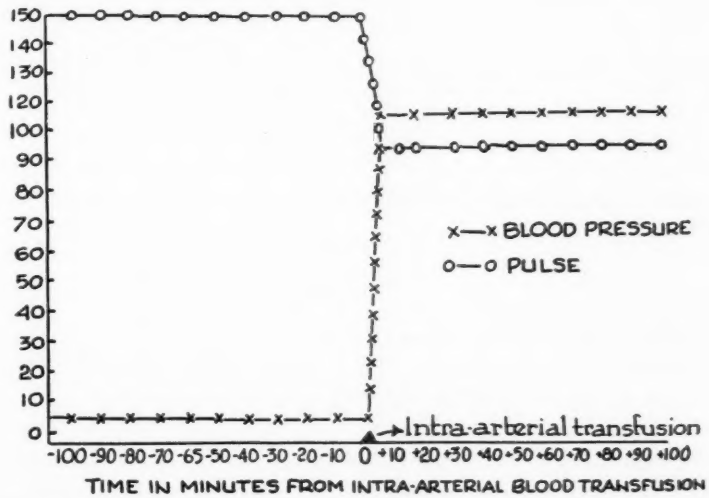

Fig. 1.—Average response of pulse and blood pressure to intra-arterial transfusion in 9 cases.

The hypogastric artery has been used by our service previously and we would prefer to use it if we are dissecting deep in the pelvis as in pelvic exenteration or other types of extensive pelvic surgery. The advantage of the hypogastric is obvious in that it can often be ligated with impunity if need be.

It has been our practice never to close the abdomen while the patient is still in shock. With his hand on the aorta the surgeon can often tell better than the anesthesiologist what the actual condition is and he has exposed a pathway to give another intra-arterial transfusion if needed. With the abdomen closed and the patient still in shock the surgeon may further be undecided as to whether intra-abdominal bleeding is still present. Therefore we wait until the patient is recovering from shock before closing the abdomen.

Many intricate and handy devices used for intra-arterial transfusion are described in the literature. Usually these devices require someone present who knows how to operate them and that person may not be available at the

TABLE I

CASE	NUMBER	ORIGIN	DIAGNOSIS	DURATION OF HEMORRHAGE	ARTERY UTILIZED	RESULTS
1	T-48-311393	Elsewhere	Ruptured uterus	11 hours	Rt. common iliac	Lived
2	I-48-320957	Elsewhere	Ruptured ectopic pregnancy	2 hours	Lt. common iliac	Lived
3	T-47-268374	Tulane Unit	Ruptured uterus	2 hours	Rt. external iliac	Lived
4	T-42-60435	Tulane Unit	Hemorrhage at cesarean section	20 minutes	Lt. common iliac	Lived
5	T-55-186918	Elsewhere	Abruptio placentae	5 hours	Rt. hypogastric	Lived
6	T-55-181981	Elsewhere	Ruptured ectopic pregnancy	16 hours	Rt. hypogastric	Lived
7	T-52-72489	Tulane Unit	Hemorrhage at operation for tuboovarian abscess	1 hour	Lt. common iliac	Lived
8	T-55-204216	Tulane Unit	Postoperative hemorrhage, necrosis left deep epigastric artery	2 hours	Lt. external iliac	Lived
9	T-52-62379	Tulane Unit	Postmortem section	2 hours	Rt. hypogastric	Died

TABLE II

	INTRAVENOUS TRANSFUSIONS PRIOR TO INTRA-ARTERIAL TRANSFUSION				INTRA-ARTERIAL TRANSFUSIONS				
CASE	PULSE	BLOOD PRESSURE	AMOUNT (C.C.)	DURATION RX. (MINUTES)	DURATION (MINUTES)	AMOUNT (C.C.)	BLOOD PRESSURE	PULSE	TOTAL BLOOD (C.C.)
1	180	0/0	2,500* 1,000	600	3	350	140/90	96	2,500* 6,250
2	120	0/0	500* 1,000	90	2	200	120/70	80	500* 2,700
3	Irreg	0/0	2,000	60	5	350	100/82	86	3,000
4	160	0/0	1,000	10	5	500	120/80	100	2,000
5	0	0/0	1,500	45	6	1,000	90/60	90	8,500
6	180	0/0	1,000* 1,500	60	2	300	130/90	120	1,000* 2,000
7	130	0/0	1,000	45	6	500	100/80	100	2,000
8	160	40/0	1,000	90	2	300	110/70	120	2,000
9	0	0/0	500	60	6	750	100/60	120	2,000
Total	150†	4/0	10,500	1,060	37	4,250			30,450
Average			1,166	117	4.1	472	112/76	101	3,383

*Plasma expander (dextran) given until blood available.
†Average of the pulse rates recorded.

time intra-arterial transfusion is needed. In the type of cases we are describing and in a patient who is ill enough to require an intra-arterial transfusion, the surgeon does not have time to instruct in the usage of a complicated device. Our equipment has been an ordinary transfusion set. The outer surface of the polyethylene tubing may not be sterile but we must disregard this, as a rigid aseptic technique is not of prime importance at this critical moment. Simplicity is the keynote. An untrained nurses' aide can pump the sphygmomanometer bulb which is attached to the transfusion bottle by a glass adapter and an 18 gauge needle. One must continually observe the tubing for air in the system for, as previously emphasized, the danger of air embolism is ever present.

Table I is a summary of nine cases in which intra-arterial blood transfusions have been used in the past 4 years. The origin, type of pathology, duration of hemorrhage, artery utilized, and final results are shown for each patient to whom intra-arterial transfusion was given. In the majority of cases, the disease process was of such a nature that massive hemorrhage was the result and the most expeditious method of restoring circulatory equilibrium and replacing blood loss was indicated.

Table II shows the amount of blood and response in each case with the use of intravenous and then intra-arterial transfusions. The duration and amount of each intravenous transfusion may be contrasted with the duration and amount of intra-arterial transfusion as indicated by the blood pressure and pulse response shown during intravenous transfusion and following intra-arterial transfusion. Following an average of 472 c.c. of blood given intra-arterially over an average time interval of only 4.1 minutes the average blood pressure increase was from 4/0 to 112/76, with a corresponding average pulse reduction from 150 to 101 per minute (Fig. 1). In all cases there was a failure of clinical response when intravenous transfusion of blood under maximum amounts of pressure was used. The reversal of circulatory collapse within minutes following initiation of intra-arterial transfusion, with a return to normal range of both blood pressure and pulse and a corresponding improvement in general clinical condition with no instance of circulatory overload, is certainly an argument for the efficacy of this procedure in the patients on whom it was utilized. Intra-arterial transfusion is primarily to restore circulatory equilibrium and intravenous transfusion is to be continued until blood loss has been replaced.

Comment

The fact that blood can be safely administered by the intra-arterial as well as the intravenous route should be recognized by all who are in surgical specialties and have to deal with unexpected blood loss and patients in severe shock from hemorrhage. Should severe shock from hemorrhage occur, or be present, at the time of laparotomy, it is to be remembered that the surgeon has at his command some of the largest blood vessels in the body available for transfusion. From our own and the experience of others the administration of blood into an artery produces more rapid results with a smaller volume introduced than if larger amounts were administered intravenously. We have utilized intra-arterial transfusion in cases of severe shock and found the procedure to be lifesaving. We have noted no ill effects. The danger of tissue necrosis due to vasospasm occasioned by the trauma of introducing a needle into an artery can be minimized by spraying the artery with a local anesthetic following completion of the intra-arterial transfusion. Regional sympathetic block can be utilized if the former fails completely to relieve vasospasm.

Conclusions

1. On the basis of our results in cases of severe shock due to hemorrhage we find intra-arterial transfusion to be a lifesaving procedure.

2. Profound shock can be better combated by administration of blood into the arterial tree, especially if there is a failure of response to intravenous blood transfusion.

3. The possibility of the utilization of intra-arterial transfusion should be uppermost in the minds of anyone having to deal with hemorrhage.

References

1. Halsted, W. S.: New York M. J. **38**: 625, 1883.
2. Veal, J. R., Russell, A. S., and Stubbs, D.: Am. Surgeon **18**: 1150, 1952.
3. Kohlstaedt, K. G., and Page, I. H.: Arch. Surg. **47**: 178, 1943.
4. Hackel, D. B., and Goodale, W. T.: Circulation **11**: 628, 1955.
5. Salisbury, P. F.: Circulation Res. **3**: 633, 1955.
6. Wolff, F. W.: Lancet **2**: 72, 1954.
7. State, D., and Salisbury, P. F.: Surg., Gynec. & Obst. **103**: 202, 1956.
8. Veal, J. R., Dugan, T. J., Bauersfeld, R., and Russell, A. S.: South. M. J. **44**: 1096, 1951.
9. Haxton, H. A.: Lancet **1**: 622, 1953.
10. Choo, L. W.: Yokohama M. Bull. **4**: 298, 1952.
11. Bingham, D. L. C.: Lancet **2**: 157, 1952.
12. Robertson, G.: Surg., Gynec. & Obst. **87**: 694, 1948.
13. Maloney, J. V., Jr., Smythe, C. M., Gilmore, J. P., and Handford, S. W.: Surg., Gynec. & Obst. **97**: 529, 1953.
14. Case, R. B., Sarnoff, S. J., Waithe, P. E., and Sarnoff, L. C.: J. A. M. A. **152**: 208, 1953.
15. Artz, C. P., Sako, T., and Brownell, A. W.: U. S. Armed Forces M. J. **6**: 313, 1955.
16. Porter, M. R., Sanders, E. K., and Lockwood, J. S.: Ann. Surg. **128**: 865, 1948.
17. Yee, J., Westdahl, P. R., and Wilson, J. L.: Ann. Surg. **136**: 1019, 1952.

ELECTROMYOGRAPHY OF THE HUMAN UTERUS

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SINCE the classic experiments of Schatz[11] in 1872 in which he recorded intrauterine pressure changes during labor by means of a balloon inserted into that viscus, numerous studies of uterine motility have been reported, involving a variety of techniques. These have included the use of balloons,[15] catheterization of the amniotic sac,[3] microballoons inserted into the uterine musculature,[1, 2] the use of minute intramuscular pressure receptors,[7] the placement of abdominal electrodes,[6, 8, 9, 12, 13] and studies employing the tokodynamometer.[10]

Experience in the development of practical electromyographic methods for the routine clinical study of the urinary bladder and ureter[4, 5, 14] suggested the extension of such an approach to studies of bioelectric potentials emanating from the uterine musculature. Since it was our desire to evaluate variations in activity of the human uterus as influenced by the menstrual cycle, gestation, and the menopause, an electromyographic technique was considered desirable. The insertion of balloons or the use of transabdominal needles was deemed impractical for routine use and such techniques would be inapplicable to the nongravid viscus and in early pregnancy. Moreover, conclusions based on the use of abdominal or other electrodes not in direct contact with the uterus might be subject to misinterpretation due to artifact emanating from the bioelectric activity of underlying muscles and viscera. It was further considered that the tokodynamometer could not be utilized in the nongravid uterus nor in early pregnancy, and that it yields a mechanogram of abdominal wall movement rather than a record of bioelectric activity within the uterine musculature which was to constitute the subject of the projected study.

With these points to be considered, an attempt was made to devise a method for recording spontaneous bioelectric potentials from the uterus which would be simple, nontraumatic, and adapted to studies on the nongravid uterus and during any stage of gestation as well.

Methods

Recordings were made in the outpatient clinic from the nongravid and gravid uterus as shown schematically in Fig. 1. It had been ascertained in former studies on the urinary bladder and ureter[4, 5, 14] that abdominal muscle tension in an anxious patient undergoing an unfamiliar procedure may frequently produce visceral movement synchronously with the respiratory cycle,

resulting in consequent artifact in the electromyogram. Therefore simultaneous respiratory records were secured in all instances by means of a thermocouple placed over the patient's nares, the currents generated by fluctuations in air temperature with each respiratory cycle being amplified in the ink-writing oscillograph employed. It is our confirmed belief that a correct interpretation of any visceral electromyogram obtained in situ cannot be made unless such records are accompanied by a simultaneous respiratory tracing.

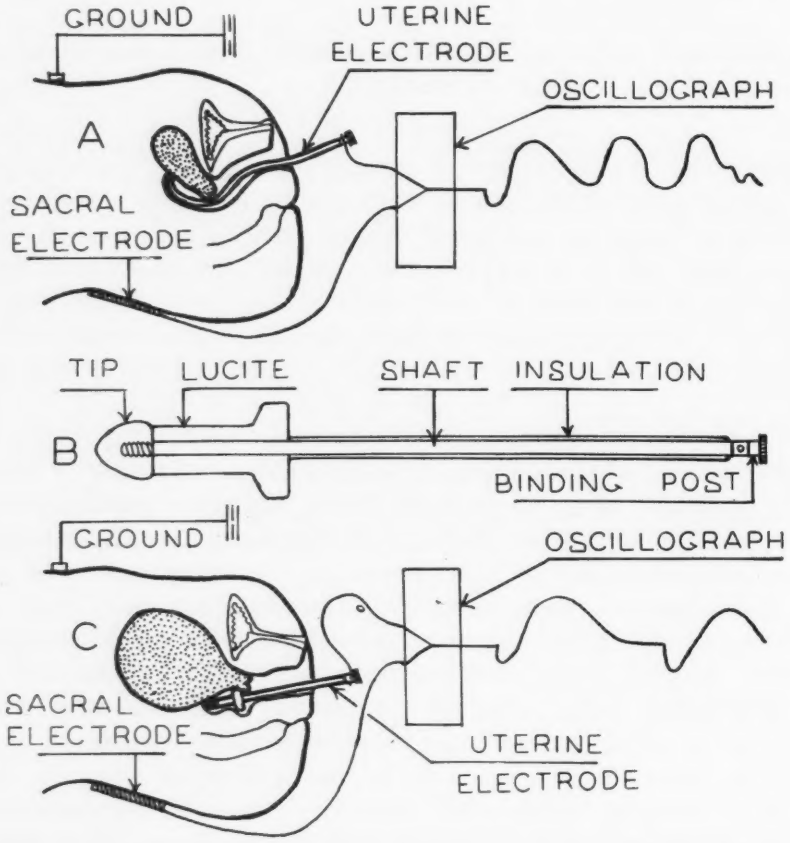

Fig. 1.—Schematic diagram of the method employed in obtaining uterine electromyograms in situ. *A*, Showing application of electrode at the mid-body of the uterus in the nongravid organ. *B*, Detailed sketch of an electrode suitable for recording from the gravid uterus. *C*, Illustrating the necessity for modification in electrode design as gestation progressed.

During preliminary trials, a paper speed of 6.0 mm. per second was found to be optimal and thereafter was adhered to in recordings from 40 clinic patients. As in earlier work noted above, it was found desirable to employ knee rests on the examination table, well padded with sponge rubber to assure maximal comfort, and particular effort was made to maintain an atmosphere of calm and quiet in the room, in which subdued lighting was used. Patients in whom undue apprehension or discomfort was apparent during the recording period were excluded from the study. A similar technique was employed in obtaining myograms from women in labor. In the operating room, specially adapted bipolar electrodes were applied directly to the surface of the uterus at hysterectomy or cesarean section.

In these experiments a sacral (indifferent) electrode (13 by 13 cm.) of polished copper was coated with a conducting paste and slipped beneath the patient, being held in place by the subject's weight. A small (6 mm. diameter) silver ground electrode was applied to the abdomen in the midline 5 to 10 cm. above the umbilicus and held in place by adhesive tape. This precaution had been found[4, 5, 14] quite satisfactorily to eliminate cardiac potentials from appearing in the records.

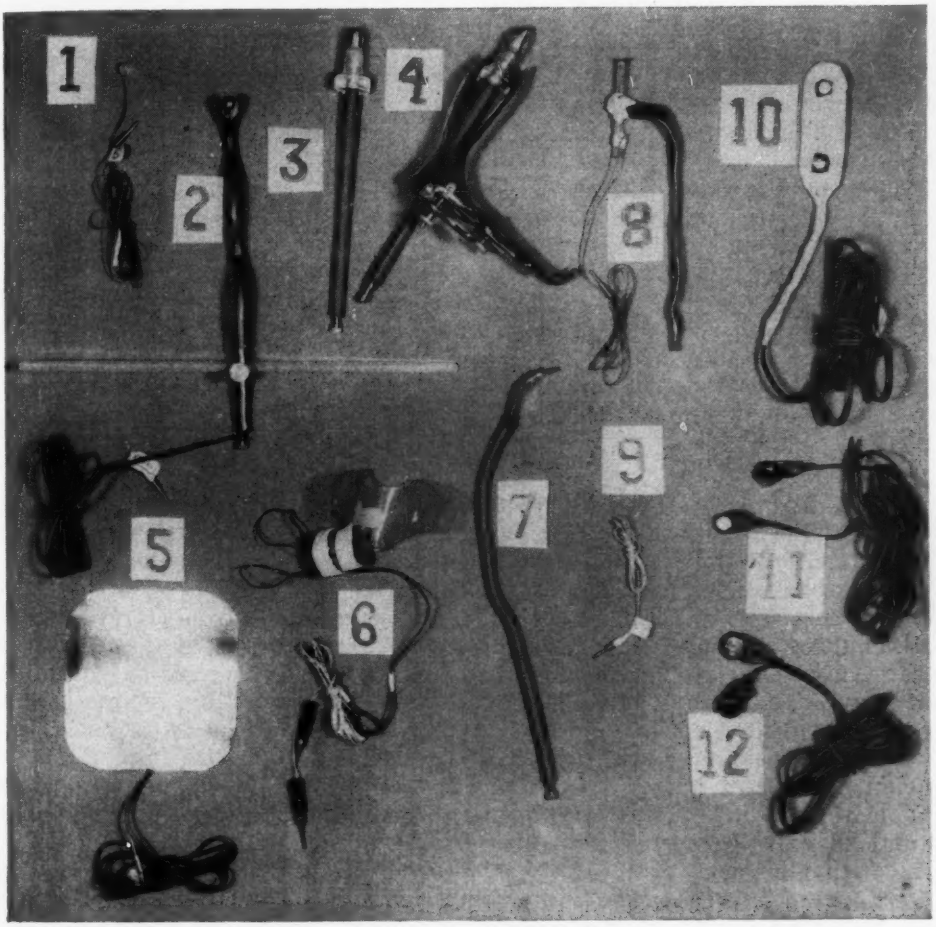

Fig. 2.—Electrodes used in recording electropotential changes in the human uterus. *1*, Ground electrode placed on the midline of the abdomen 5 to 10 cm. above the umbilicus. *2*, Uterine electrode for recording from the nongravid uterus. *3* and *4*, Electrodes for use during gestation. Number 4 illustrates placement of electrodes through a standard vaginal speculum. *5*, Sacral (indifferent) electrode. *6*, Thermocouple placed over nares for synchronous recording of respiration. *7*, Electrode for use during labor. *8*, Contact for recording from excised whole uteri. *9*, Contact for recording from isolated uterine strips. *10*, Double-contact electrode for direct anterior placement of uterus during vaginal hysterectomy. *11* and *12*, Double-contact electrodes for use at cesarean section.

The uterine electrodes were of diverse design (Fig. 2), modified by trial and error following numerous fittings. Those used in the clinic were of brass and copper, silver plated, with the shaft insulated by means of rubber tubing and with a binding post at the extremity proximal to the operator. Sterilization was by autoclave and the electrodes were kept ready for use in Zephiran solution. A single design sufficed for recordings from the nongravid uterus, but

anatomical changes accompanying the progress of gestation necessitated alteration in order to maintain contact with the body of the uterus (Fig. 1). In use, the proper electrode was introduced through a standard vaginal speculum and placed sufficiently high in the posterior fornix to contact the uterus at approximately its mid-point. This deep placement was found essential, since no bioelectric potentials could be recorded from the cervix in any instance. Hence, in the event that an electrode slipped and lost direct contact with the body of the uterus, one was at once made aware of the fact by the absence of the smooth muscle potentials on the record. The potential differences between the uterine and sacral electrodes were recorded as the uterine electromyogram.

Since the validity of records obtained in situ might be subject to question on the ground that they could be affected by electropotentials emanating from adjacent viscera such as the urinary bladder, bowel, or vagina, 13 uteri were obtained at hysterectomy from which strips of muscle were excised. These were suspended in oxygenated Locke's solution at 37° C. and electromyograms were obtained through fine silver wire electrodes for purposes of comparison with those secured in situ. In addition, 11 whole uteri were suspended in a moist chamber at body temperature and records secured through silver disk electrodes placed in contact with the uterine musculature.

At hysterectomy or cesarean section, the sacral electrode was grounded, and bipolar electrodes were placed in direct contact with the body of the uterus while its position and blood supply were intact. In these instances the records represented differences in potential between the ground and the upper and lower segments of the viscus.

Results

The Nongravid Uterus.—Fig. 3 illustrates the character of the records secured from the nongravid uterus at different time periods following the onset of menstruation. It will be noted that they are predominately monophasic deflections which we have arbitrarily characterized as "C" waves, in conformity with a terminology adopted by one of us in a series of electromyographic studies of the human urinary bladder and ureter.[4, 5, 14] Occasional biphasic potentials were recorded in 6 of 12 women of this series, but these occurred so infrequently that it appeared that the monophasic C wave was typical and characteristic of the nongravid uterus.

There was no significant difference in the potentials developed during the ovarian cycle, and indeed the postmenopausal viscus was found to be quite capable of bioelectric activity of an intensity equal to that recorded from women 22 and 23 years of age, as shown in Fig. 3, *F*. In this respect it should be recalled that bioelectric potentials as recorded are not invariably proportional to the force of muscle contraction—a fact well known to the cardiologist. However, potentials as we have recorded them were sufficiently uniform that we were able to employ the same degree of amplification in all of our records from the uterus in situ. It is our wish, nevertheless, to minimize the physiologic importance of the magnitude of potential changes in any such myographic studies, for they would depend in large measure on electrical resistance, and thus upon electrode surface area, efficiency of the electrode-muscle contact, etc.

On the other hand, analysis of the records disclosed marked differences in frequency of electrical discharge (Fig. 4). Thus, from 3 to 8 days after the onset of menstrual bleeding, the frequency of electropotential shift averaged 5.8 per minute, while at 17 days this had fallen to 2.0 per minute. As the anticipated onset of the next menstruation approached (28 days), frequency of potential change had increased to 5.6 per minute.

It was concluded that frequency of the uterine bioelectric activity is highest in the nongravid organ just prior to, during, and immediately subsequent to

endometrial sloughing, and minimal at the mid-point of the cycle. This minimal activity coincides with ovulation and, as will appear later, a lowered rate of activity is maintained throughout a pregnancy when this occurs (Table I). Such a situation should favor implantation and subsequent placentation.

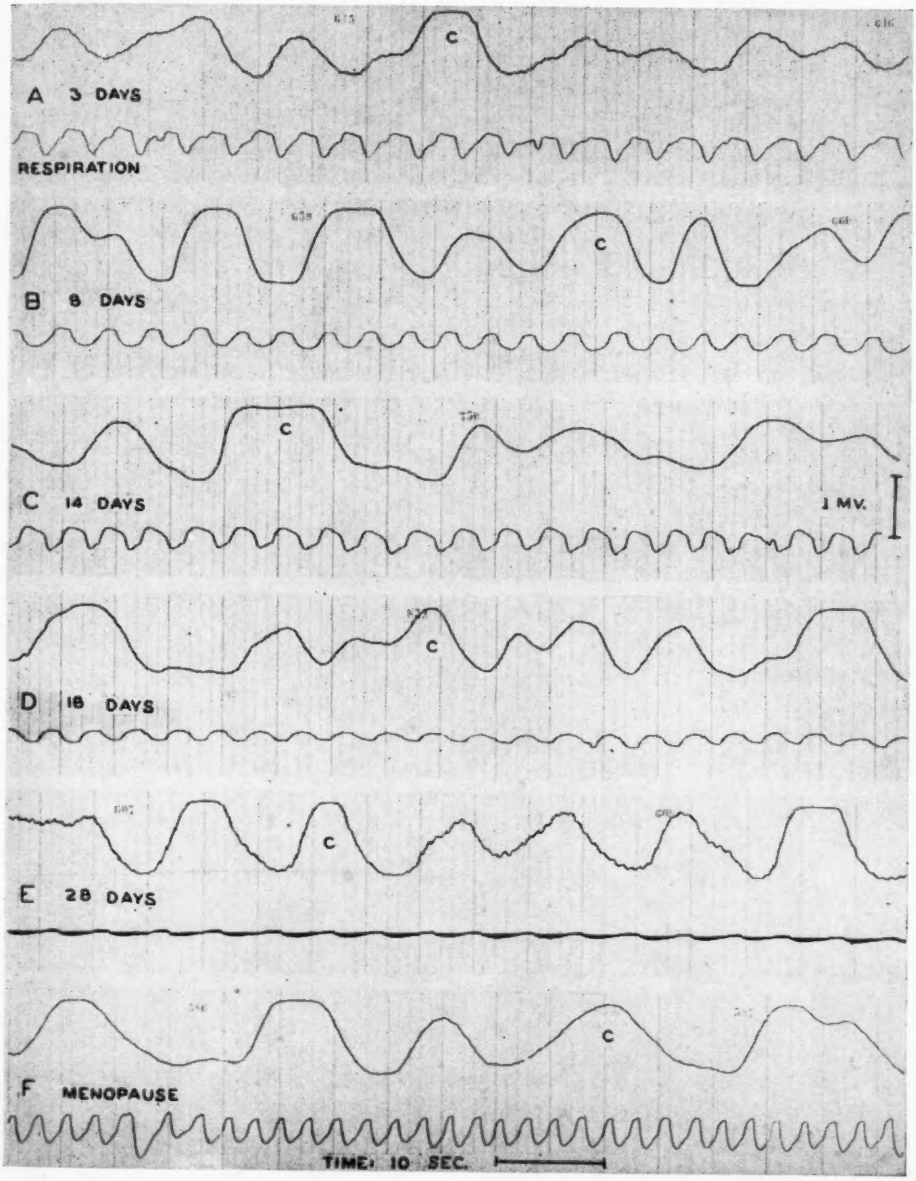

Fig. 3.—Electromyograms secured at various periods during the menstrual cycle. Deflections are monophasic throughout. Note synchronous recordings of the patients' respiration in each instance, a procedure essential for the detection of artifact due to transmitted mechanical movement should it occur. The menopausal uterus (*F*) shows pronounced bioelectric activity.

The Gravid Uterus.—Electromyograms were obtained from a series of 25 gravid women, representative records from whom are shown in Figs. 5 and 6. It was at once apparent that the potential changes recorded were predominantly of the biphasic type, a wave form which we have designated "A" and

TABLE I. AVERAGE VALUES OBTAINED FROM ANALYSIS OF ELECTROUTEROGRAMS OBTAINED FROM NONGRAVID AND GRAVID UTERI IN SITU, AS WELL AS FROM ISOLATED HUMAN UTERINE STRIPS

NO. CASES	AGE	DAYS SINCE ONSET LAST MENSTRUAL PERIOD	FREQUENCY POTENTIAL (CHANGE/ MIN.)	DUR. A-B COMPLEX WHEN PRESENT (SEC.)	DUR. A WAVE (SEC.)	DUR. B WAVE (SEC.)	DUR. C WAVE (SEC.)	DUR. D WAVE (SEC.)	E.M.F. A WAVE (MV.)	E.M.F. B WAVE (MV.)	E.M.F. C WAVE (MV.)	E.M.F. D WAVE (MV.)	RESP. RATE MIN.
Electrouterograms Obtained in Situ													
Nongravid Series.—													
12	29.2	3-28	4.36	14.85	4.35	10.50	8.42	2.35	.374	.534	.635	.200	16.45
Gravid Series.—													
25	25.5	30.9 weeks' gestation (14-42)	2.70	11.60	2.90	8.70	6.70	2.60	.278	.420	.334	.163	20.10
Electromyograms Obtained From Isolated Uterine Strips													
13	37.0	Nongravid	12.10	3.40	0.90	2.50	2.52	0.84	.114	.201	.211	.022	

"B" deflections, the A wave being of lesser potential and duration than the B. This type of record is also characteristic of other viscera, i.e., the urinary bladder and ureter.[4, 5, 14] in Figs. 5, *B* and 6, *J* a small precursory deflection may be noted, which we designate "a." Artifacts in the tracing are also clearly shown in record Fig. 5, *B* (*R*), coinciding with the phases of respiration, and such deflections may be noted throughout record 6, *G*, superimposed upon typical A-B waves. Such "R" deflections are of course not myograms in any sense, but are entirely due to mechanical movement of the uterus with shifts in the abdominal contents coincident with the respiratory cycle. It is for this reason that we are unwilling to interpret any visceral myograms obtained in situ in the absence of synchronous respiratory records. Figs. 5, *D* and 6, *H* illustrate the occasional occurrence of C waves in records from the gravid uterus and brief, low-voltage deflections designated as "D" waves as indicated in Figs. 5, *D*, 6, *F*, and 6, *J*. A rather characteristic tendency toward a "doubling" of the A wave is illustrated in Figs. 5, *E*, 6, *F*, and 6, *J*, these wave forms occurring with such frequency that they were interpreted as being of physiologic origin.

No significant trend in the frequency of potential shift was evident throughout this series (14 to 40 weeks' gestation), but average frequency was lowered by 36 per cent from that observed in the nongravid uterus. Moreover, both the duration and potential of all wave complexes were found, on the average, to be reduced in pregnancy.

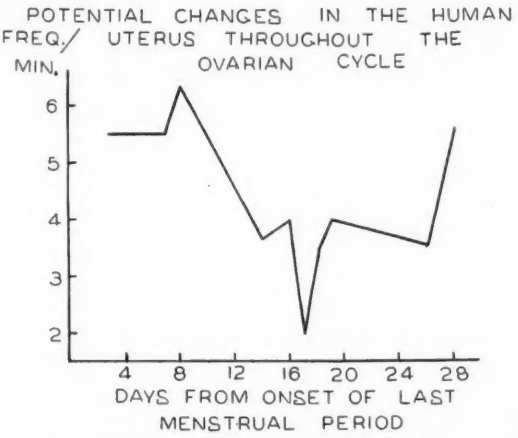

Fig. 4.—Frequency of electropotential changes in the nongravid human uterus throughout the ovarian cycle.

Isolated Uterine Muscle.—In the interpretation of any visceral electromyograms obtained in situ, the question ultimately arises as to whether the records produced are actual representations of bioelectric potentials arising within a specific organ, or are in part influenced by the activity of adjacent viscera, in this case the bladder and lower bowel. For this reason a series of muscle strips was excised from 13 uteri and suspended in oxygenated Locke's solution at 37° C. Recordings were secured through fine silver wires attached at the extremities of these tissue strips, as shown in Fig. 7.

It will be noted in all of the nongravid uteri studied, that C and D deflections predominated as in the records secured in situ. Occasional A-B deflections occurred as in tracing 7, *D*, 7, *F*, 7, *I*, and 7, *J*, but such wave complexes were infrequent. All of the wave forms observed in the tracings secured in situ were duplicated in these records and this fact was interpreted as evidence

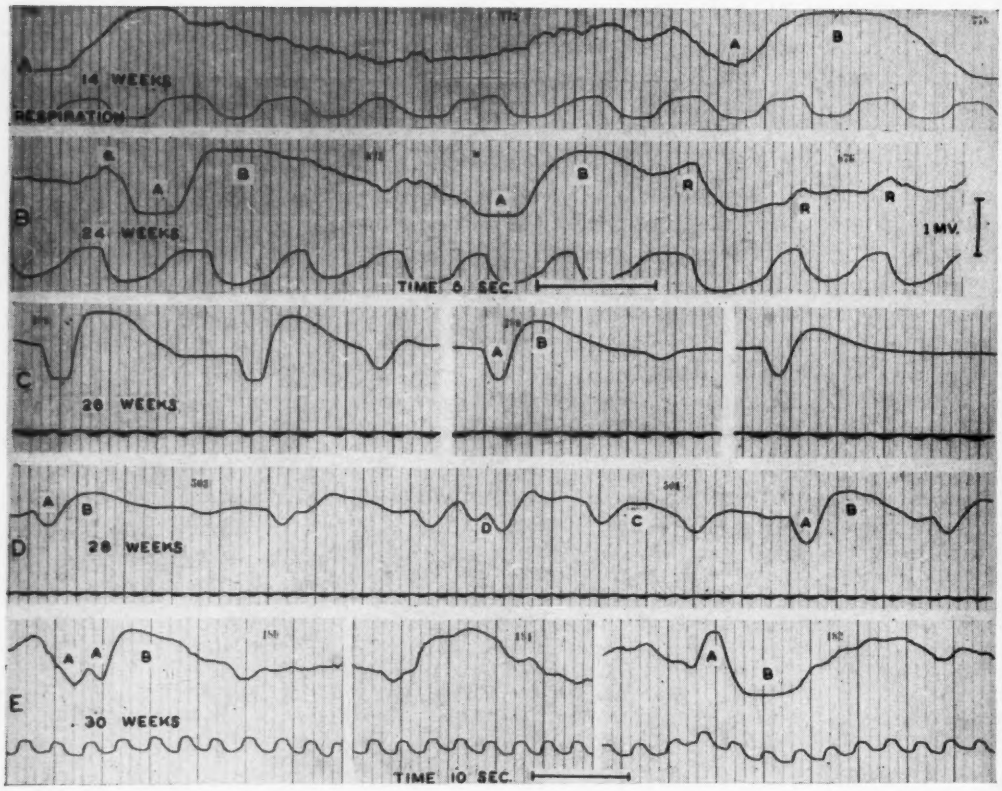

Fig. 5.—Electromyograms secured from the gravid uterus in situ (14 to 30 weeks). Deflections are predominantly biphasic (*A-B*). In record *B* a small, precursory *a* wave is shown as well as artifact due to respiratory movements at *R*. A tendency for the *A-B* deflections to occur in pairs is illustrated in record *C*. Small *D* waves are shown in tracing *D*. In record *E*, paired *A* deflections are illustrated, as well as reversal of polarity at the far right.

that the former did, in fact, represent true uterine potentials. Since the muscle samples employed were excised from several different sites, it appeared that these tissues were equipotential as far as bioelectric activity is concerned.

It was, moreover, observed that such activity was by no means limited by age, as shown in records from postmenopausal uteri 7, *I*, 7, *J*, and 7, *K*, the latter tracing showing pronounced C waves at age 82 years.

The frequency of electrical discharge was found to be much augmented in these excised tissues (Table I) averaging 2.8 and 4.5 times that observed in records obtained in situ from the nongravid and gravid organ, respectively, while, as might be anticipated, electropotentials were markedly reduced.

It was concluded, on the basis of the above, that the potential shifts as recorded in situ did, in fact, represent bioelectric activity arising from the uterine musculature and were free from artifact arising from smooth muscle activity in adjacent viscera.

Comment

It may be noted that no examples of our records secured in the operating and delivery rooms are included in the above presentation. This is because synchronous respiratory tracings were found to be impractical in the former situation and because artifacts are invariably present during active labor in the latter.

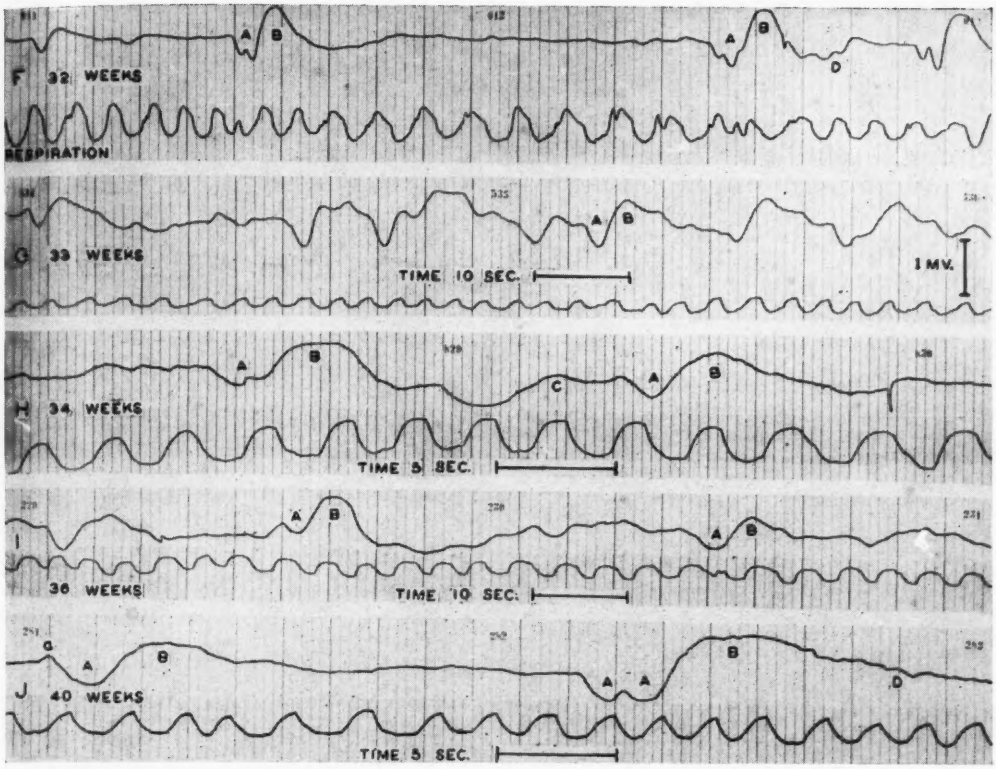

Fig. 6.—Electromyograms secured from the gravid uterus in situ (32 to 40 weeks). *A-B* deflections still predominate, and *a*, *C*, and *D* waves occur occasionally.

Since during labor the patient exhibits gross bodily movement with accompanying powerful contractions of the abdominal muscles, we were soon convinced that no true electromyographic recordings from the uterus are possible at this time. The same criticism could apply to any myographic methods such as the use of intrauterine balloons, catheters, pressure receptors, "tocometers," and the tokodynamometer. Pressure recordings can give a true picture of pressure per se only, but cannot be used as a quantitative index of the true force of uterine muscle contraction since intrauterine pressure in labor represents the sum of pressures exerted by both uterine and abdominal muscles. This same factor will apply in any recordings whether mechanical or electrical. For these reasons it appears that none of the current methods can be considered to yield quantitatively accurate data on the force of uterine contraction during terminal labor.

The resistance of isolated uterine muscle strips to anoxia was quite striking. These preparations continued to exhibit bioelectric activity of initial potential for at least 6.5 hours after oxygenation had been intentionally stopped. How much longer such activity can be maintained in the virtual absence of oxygen was not determined. Moreover, such electromyograms do not serve as an index of the force of contraction. This was shown by the fact that such preparations

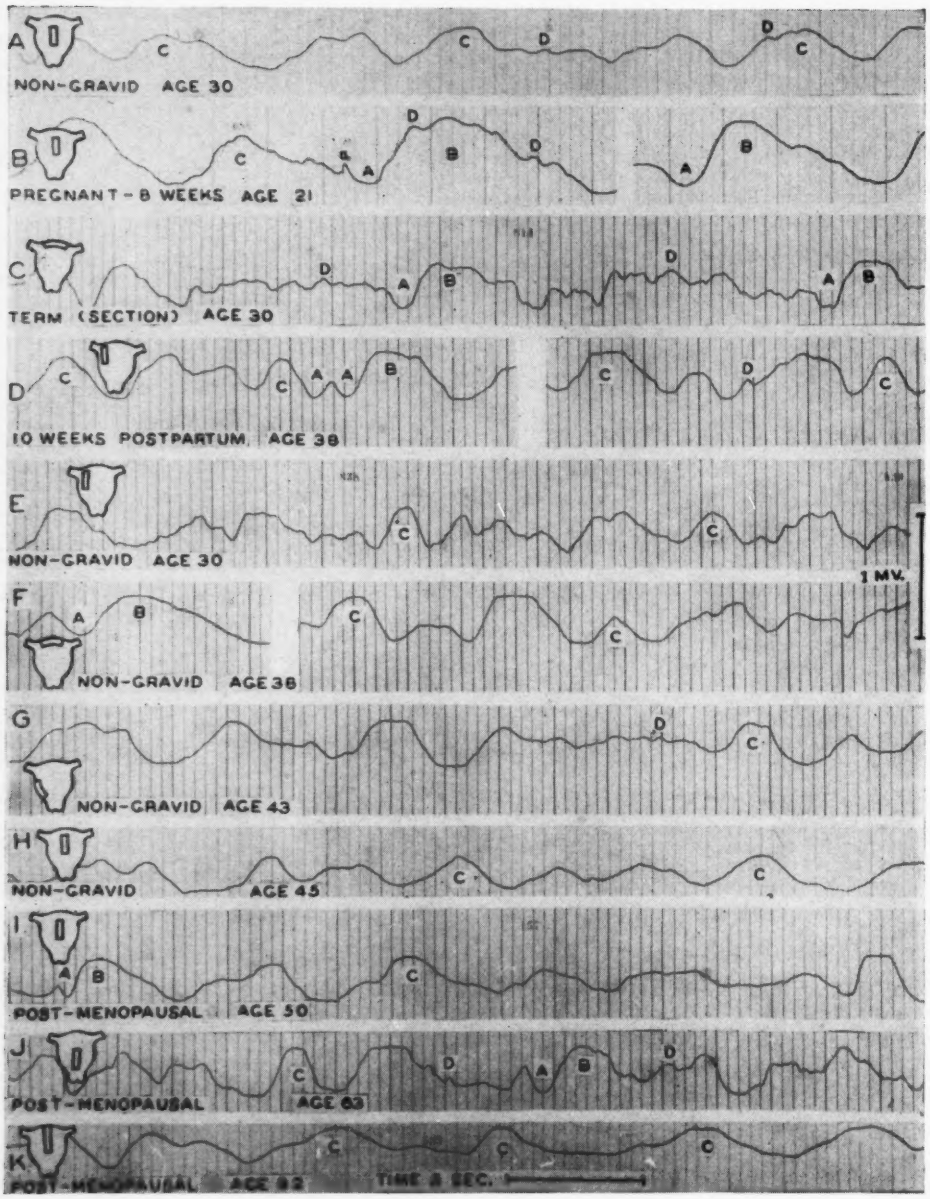

Fig. 7.—Electromyograms from isolated strips of uterine muscle excised from areas shown schematically at the left of each record.

continued in a highly active state following exposure to high (saturation) concentrations of ether within the tissue chamber. This finding alone appeared to eliminate electromyographic methods as a means of assaying the effects of anesthetics and other pharmaceutical preparations upon the uterine musculature.

Summary

1. A simple, nontraumatic method for recording bioelectric potentials emanating from the human uterus in situ is described.

2. Potential shifts as recorded from the nongravid organ were predominantly monophasic, the frequency varying with the ovarian cycle. This frequency of potential change was highest just prior to and immediately following menstruation and lowest at a time approximating ovulation.

3. Potential shifts during pregnancy were characteristically and predominantly biphasic. The frequency of such potential changes remained relatively constant throughout gestation, approximating that seen during the ovulatory phase of the menstrual cycle.

4. Records from isolated uterine muscle strips were of such a character as to be interpreted as evidence that tracings secured from the uterus in situ represented true uterine electropotential changes. These records gave indication of the equipotentiality of various portions of the uterus as regards bioelectric activity.

5. Bioelectric activity is present in the human uterus until at least the age of 82 years.

The Grass oscillograph used in this study was lent to us by Dr. S. A. Vest of the Department of Urology. Its purchase had been made possible through the generosity of Dr. J. W. Crosson of G. D. Searle & Co., Chicago, for which we wish to express our appreciation and thanks.

References

1. Alvarez, H., and Caldeyro-Barcia, R.: Proc. First World Conference on Fertil. and Steril., Mexico, 1953, Editorial Jus, p. 217.
2. Caldeyro, R., Alvarez, H., and Reynolds, S. R. M.: Surg., Gynec. & Obst. **91**: 641, 1950.
3. Carey, H. M.: J. Obst. & Gynaec. Brit. Emp. **61**: 59, 1954.
4. Corey, E. L., Boyce, W. H., Vest, S. A., and French, C. R.: J. App. Physiol. **3**: 631, 1951.
5. Corey, E. L., Fite, E. H., and Vest, S. A.: J. Urol. **75**: 244, 1956.
6. Halliday, E. C., and Heyns, O. S.: J. Obst. & Gynaec. Brit. Emp. **59**: 309, 1952.
7. Karlson, S.: Acta obst. et gynec. scandinav. **28**: 209, 1943.
8. Larks, S. D.: Federation Proc. **15**: 116, 1956.
9. Levy-Solal, E., Morin, P., and Zacouto, F.: Presse méd. **60**: 1335, 1952.
10. Reynolds, S. R. M., Heard, O. O., Bruns, P., and Hellman, L. M.: Bull. Johns Hopkins Hosp. **82**: 446, 1948.
11. Schatz, F.: Arch. Gynäk. **3**: 58, 1871-1872.
12. Steer, C. M., and Hertsch, G. J.: Am. J. Obst. & Gynec. **59**: 25, 1950.
13. Steer, C. M.: Am. J. Obst. & Gynec. **68**: 867, 1954.
14. Vest, S. A., and Corey, E. L.: Trans. Am. A. Genito-Urin. Surgeons **45**: 84, 1953.
15. Woodbury, R. A., Hamilton, W. F., and Torpin, R.: Am. J. Physiol. **121**: 640, 1938.

THE ENDOCRINE CONTROL OF MYOMETRIAL CONTRACTILITY IN THE UTERUS OF THE PREGNANT RABBIT

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(From the Rockefeller Institute for Medical Research)

THE problem of the maintenance and termination of pregnancy was considerably clarified by the discovery of the second ovarian hormone, progesterone, mostly through the work of Corner and his associates,[1] recently reviewed by Csapo.[5] In subsequent years, however, the significance of progesterone in pregnancy—especially in the human—became somewhat dubious, owing partly to lack of knowledge about cellular function and the mechanism of hormone effects, partly to the great complexity and interplay of functions involved in human pregnancy and labor. Discrepancies in experimental data and interpretations led to an indecisive attitude among clinicians concerning the role of progesterone in normal and pathological pregnancies.

Studying the contractile system of the myometrium, its energy stores, its ionic constituents and gradients across the cell membrane, Csapo[5] and his colleagues have considerably increased our knowledge concerning myometrial function and the mechanism of steroid effects, thereby also elucidating the problem of the endocrine control of pregnancy and parturition.

The hormonal status of the myometrium in any given physiological conditions can be evaluated by comparing its behavior with that of the ovariectomized rabbit, treated with known amounts of crystalline steroids.[2, 4, 7, 8, 9] In earlier experiments the endocrine state of the myometrium was inferred from inspection of the ovaries, the vaginal smear, the endometrium, or by pharmacological reactivity of the uterus.[10] Csapo[5, 6] studied the rabbit myometrium in pregnancy by in vitro techniques and found that the six different tests applied by him to distinguish between estrogen and progesterone domination gave similar results.

The work to be reported here is an in vivo study of the hormonal status of the myometrium in intact rabbits during pregnancy. A special aim is to elucidate the time scale of the endocrine shift in the myometrium at the end of gestation.

Methods

Adult New Zealand white rabbits, from the same stock, were used. Mating was observed and the exact time and date recorded. The period of 24 hours after mating was counted as day 1. In this strain, gestation lasts for 32 days.

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All the experiments were performed under light Nembutal anesthesia administered intravenously. Deeper anesthesia was necessary only during the operation and the insertion of the recording instrument. According to the experience of this laboratory, Nembutal is preferable to urethan, since the latter brings about a gradual deterioration of the experimental animal.

Light anesthesia could be better maintained and the animals lay more quietly on the operating table when tracheotomy was also employed. This operation was therefore performed at the beginning of each experiment.

The abdomen was opened by a midline incision. In pregnant animals, the conceptus at the vaginal end of one horn was displaced into the vagina and was then delivered by slight pressure from above. From the emptied segment a suitable portion at "resting length" of 1.5 to 2.5 cm. was used in the experiment. Resting length is defined according to Csapo and Goodall.[7]

Isometric tension was always recorded and maximum working capacity determined.[4]

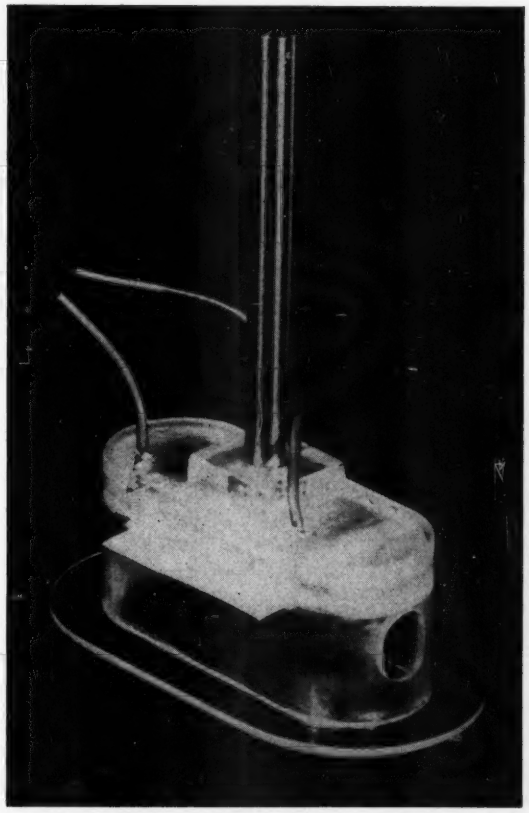

Fig. 1.—The polyethylene chamber with a filter paper inserted below the heating coil in the top of the chamber.

The instrument was a substantial modification of that described by Schofield.[8, 9] A polyethylene chamber (Figs. 1-3) was inserted through the midline incision into the abdomen. The parietal peritoneum covering the rim of the chamber, the rectus abdominis muscles, and the skin were tightened around the body of the chamber by surgical suture (Fig. 3). The uterine segment to be recorded from was suspended horizontally between two thin, double-pronged steel hooks, inserted through the holes at the two opposite ends of the chamber. The segment was only slightly elevated to keep physiological conditions as little changed as possible, while friction between the

uterine segment and the intestines was avoided. The segmental arrangement of the nerves and blood vessels reaching the uterine horn by way of the broad ligament allowed recording from the uterus in this special position without interference with innervation or blood supply. Hook *A* was fixed at one end to the uterine segment and at the other to a rack and pinion which moved on a horizontal bar, allowing accurate adjustment of the uterine segment to any desired length. Hook *B* was connected at one end to the uterine segment and at the other, through a lever system, to a Grass strain gauge, type FT10. The gauge in turn was connected to a Sanborn ink recorder. The use of the strain gauge permits practically isometric recording since the shortening involved is less than 1 per cent of the resting length. The hooks were

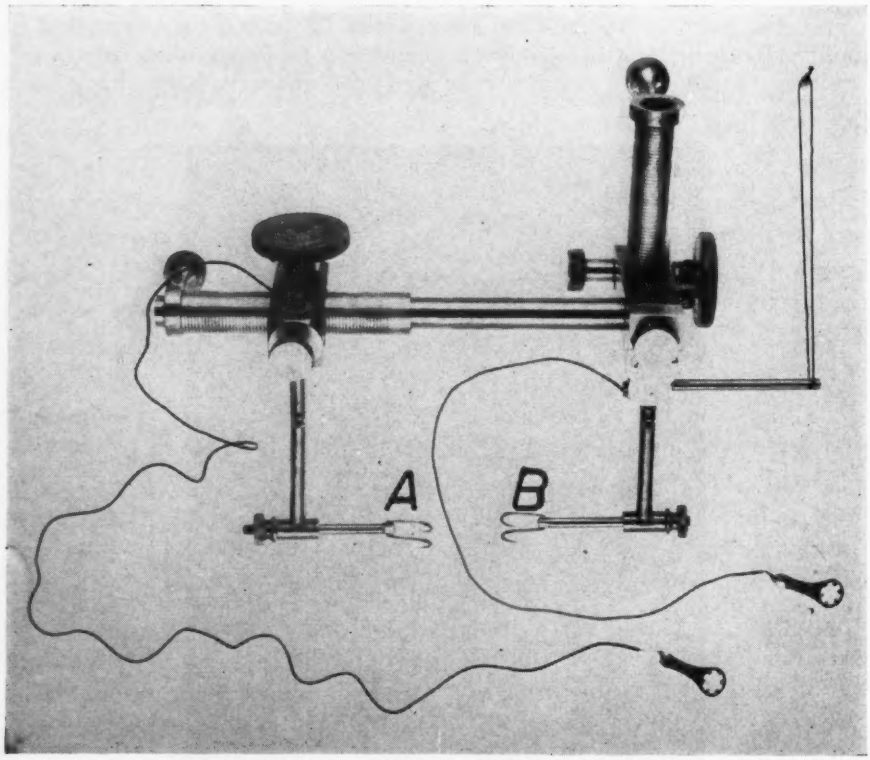

Fig. 2.—The steel hooks for recording the tension developed during uterine contractions. For description see text.

insulated from the other parts of the recording instruments and could therefore be used as electrodes for electrical stimulation. The experience of this laboratory is that the most convenient way of electrical stimulation, producing the least harmful effects, is the utilization of a 60 cycles per second alternating sinusoidal current, supplied from the house mains and controlled by a variable transformer for strength, and by a timer for duration and repetition frequency.

Extreme care was taken to keep the body temperature of the animal and also the chamber temperature constant at 38° C. The first problem was solved by the use of heating bulbs inside the operating table, the second by having a heating coil at the top of the chamber with a filter paper below it, which was kept wet with isotonic saline throughout the experiment in order to avoid its drying effect on the uterine segment. Thus the uterus was kept essentially in a moist chamber at body temperature. The rectal temperature of the animal and the temperature of the chamber were continuously recorded by thermometers.

Altogether 50 pregnant rabbits were used in these experiments. About half of them were used in establishing the reliability and the repeatability of the method. The other half were then used without further changes of method to study the endocrine control of the rabbit myometrium during pregnancy. The series of tests to which the uterine segment was subjected were in all experiments carried out in a strict order, as follows:

1. Spontaneous Activity.—When the animal had recovered from the deeper anesthesia used during the operation, and her body temperature and the temperature in the chamber had become constant at 38° C. (after about 15 minutes) the tension developed by spontaneous contraction was recorded. At the same time the resting length of the uterine segment was determined by applying small (1 mm.) stretches until resting tension had been recorded, as indicated by a rise in the base line. Since spontaneous activity is often not completely regular it was recorded for at least 30 minutes, to establish a characteristic pattern.

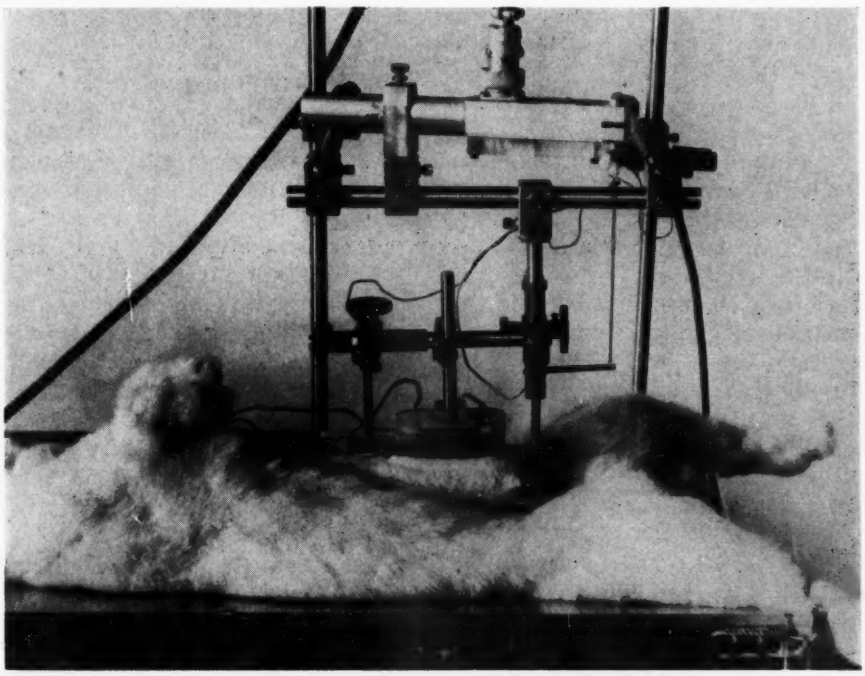

Fig. 3.—The recording instrument in situ.

2. The Relation of Tension to the Strength of Stimulation.—Electrical stimulation was applied every minute. The optimum duration of the stimulus was found to be 5 seconds, as in previous experiments in vitro.[7] This long duration is necessitated by the relatively slow development of the "active state" in the myometrium, determined by "quick release" studies.[7] After the optimum duration had been determined it was always kept constant at 5 seconds and only the strength of stimulation was varied by 1 volt steps, working upward from 1 volt.

In all experiments, tension increased asymptotically as the strength of stimulus increased, and in most cases maximum tension was obtained at 5 volts per centimeter stimulation strength. This is a considerably higher value than that required to elicit maximum tension in vitro. (Csapo[3] used 2 volts per centimeter as optimum.)

The difference in optima of stimulation strength can be explained by considering that in the in vitro experiments the muscle was stimulated at every

point simultaneously in a uniform electric field, whereas in the present experiments it was stimulated only at the two ends with what were essentially point electrodes. Moreover, a complete or partial block in conduction (as is the case in the pregnant myometrium[3]) abolishes or reduces the effectiveness of stimulation, if applied at the ends of the muscle. This particular point is of specific significance in experiments with uterine segments completely blocked by progesterone, and when the electrode distance is relatively large (as is the case in animals in early pregnancy).

When the strength of the stimulus is increased above a value of 5 volts per centimeter the electrical current spreads from the stimulating points and muscles other than the myometrium respond. Strong currents had therefore to be avoided in these experiments.

3. The Duration of a Single Contraction Cycle.—The optimum field strength having been established, stimulation was suspended for about 15 minutes until spontaneous activity resumed its original pattern. Then an optimum stimulus was applied to study the shape and duration of a single contraction cycle. To increase the accuracy of the measurements the paper speed was increased sixty fold.

4. The Staircase.—As in previous in vitro experiments,[2] two methods were employed in studying the staircase. Keeping the stimulus at optimum in one case, the muscle was stimulated repeatedly at regular 1 minute intervals after a period of 10 minutes of rest. Under these conditions, tension increases with repeated stimulation if the uterus is dominated by estrogen (positive staircase), whereas tension decreases if the uterus is dominated by progesterone (negative staircase). The other method is to elicit steady-state tension by stimulation at 30 second intervals (a higher frequency cannot be used because the contraction cycle is longer than 30 seconds), and then increase the interval in steps, i.e., 30-60-120-240 seconds, recording the tension developed at each of these frequencies repeatedly. Under estrogen domination, tension decreases with decreasing frequency of electrical stimulation (positive staircase), whereas, under progesterone domination, tension increases (negative staircase). The staircase is "transitory" (presumably owing to a change in endocrine conditions) when it is partly positive and partly negative or when it is neither positive nor negative.

5. The Length-Tension Diagram.—By changing the length of the uterine segment (as described above) with the rack and pinion, the relation of muscle length to the resting tension (unstimulated muscle) and to peak tension (optimum stimulation) can be established, and thus a length-tension diagram is obtained. The experiments always began with the segment at short length being increased by 2 mm. steps. Resting and peak tension were recorded at 1 minute intervals. Changes in length had to be made quickly because the uterus is able to "adapt," if the new length is maintained for a longer period of time.

At the end of the experiment, the animal was killed by air embolism.

Results

Twenty-five rabbits at different stages of gestation and after delivery were used (Table I). In agreement with earlier in vitro experiments carried out by this laboratory,[5] the myometrium was found to be strongly progesterone dominated during the first 26 days of gestation. The progesterone domination was characterized by irregular, frequent, and weak isometric contractions, by the short duration of the single contraction cycle (18 seconds), and by the negative staircase. In early pregnancy, as indicated in the table, certain technical difficulties arose in this type of comparative study because the uterine segment is relatively thin, and therefore the amount of

muscle used was considerably less than that employed in studies at the end of gestation. The domination of progesterone being excessive, presumably owing to the relatively small quantities of estrogen in this period of gestation (as inferred from an experiment by Csapo,[7] in which pregnancy was abolished with quantities of estrogen as small as 2.5 to 5 gamma per day per 4 kilograms of body weight), conduction is completely blocked and the spreading of the stimulating current is minimal. Although the contractile capacity of the myometrium is larger than would be indicated by Table I, tension is low because of the ineffectiveness of point electrode stimulation. The maximum tension observed under these conditions was about 26 to 43 Gm. per gram of muscle (wet weight). Spontaneous isometric contractions attained only about 15 per cent of maximum tension (Fig. 4). On the twentieth day of gestation and on the twenty-sixth day (Fig. 5) the maximum force developed is 153 to 158 Gm. per gram of muscle, and the spontaneous contractions become 30 to 40 per cent of maximum tension. In other aspects (duration of the single contraction cycle and the staircase), the picture is not significantly changed during the first 26 days of pregnancy.

TABLE I. SOME PHYSIOLOGICAL PROPERTIES OF THE RABBIT MYOMETRIUM AT DIFFERENT STAGES OF GESTATION

DAY OF GESTATION	NUMBER	TENSION DEVELOPED		DURATION OF SINGLE CONTRACTIONS IN SECONDS	SPONTANEOUS TENSION IN % OF MAXIMUM	STAIRCASE
		GM./CM.	GM./GM.			
4*	1	8.8	26	17	--	Negative
6*	1	8.6	43	18	15	Negative
20	1	62	153	18	30	Negative
26	4	87	158	17	40	Negative
29	4	83	136	24	35	Transitory
32	4	76	153	28	63	Positive
12 hours post partum	4	143	179	32	55	Positive
24 hours post partum	4	70	132	36	50	Positive
48 hours post partum	2	47	90	32	40	Positive

*These data require special consideration, for which see text.

On the twenty-ninth day (Fig. 6) a marked change in the behavior of the myometrium can be observed. Spontaneous activity is less frequent and more regular. The duration of the single contraction cycle increases from between 17 and 18 to 24 seconds and the staircase becomes transitory. Maximum tension, however, is unchanged. These changes are taken as an indication that progesterone domination is beginning to decline, an observation which is in good agreement with the finding that labor can be induced in rabbits only from the thirtieth day of gestation onward.[4] Some hours before labor (thirty-second day, Fig. 7), the changes described in the previous paragraph are further exaggerated. Spontaneous contractions are regular, infrequent, and large (63 per cent of maximum tension). The duration of the single contraction cycle increases further to 28 seconds, and the staircase is no longer transitory but positive. Maximum tension, however, is unchanged. The myometrium is clearly estrogen dominated. These changes between the twenty-ninth and thirty-second days of pregnancy are significant. Before these biological tests were developed, a shift in endocrine domination at the end of gestation was only inferred on the basis of indirect evidence. That such a shift does in fact occur in the living animal has been clearly shown both in vitro by Csapo[5] and in vivo by the present experiments. According to the tests employed in the present studies, the shift from progesterone to estrogen

domination begins on the twenty-ninth day and is completed at the thirty-second day, when labor normally occurs. The progesterone withdrawal satisfactorily explains the onset of labor in the rabbit.

At 12 hours post partum (Fig. 8), estrogen domination has further increased. Spontaneous contractions are very regular, infrequent, and strong

Fig. 4.

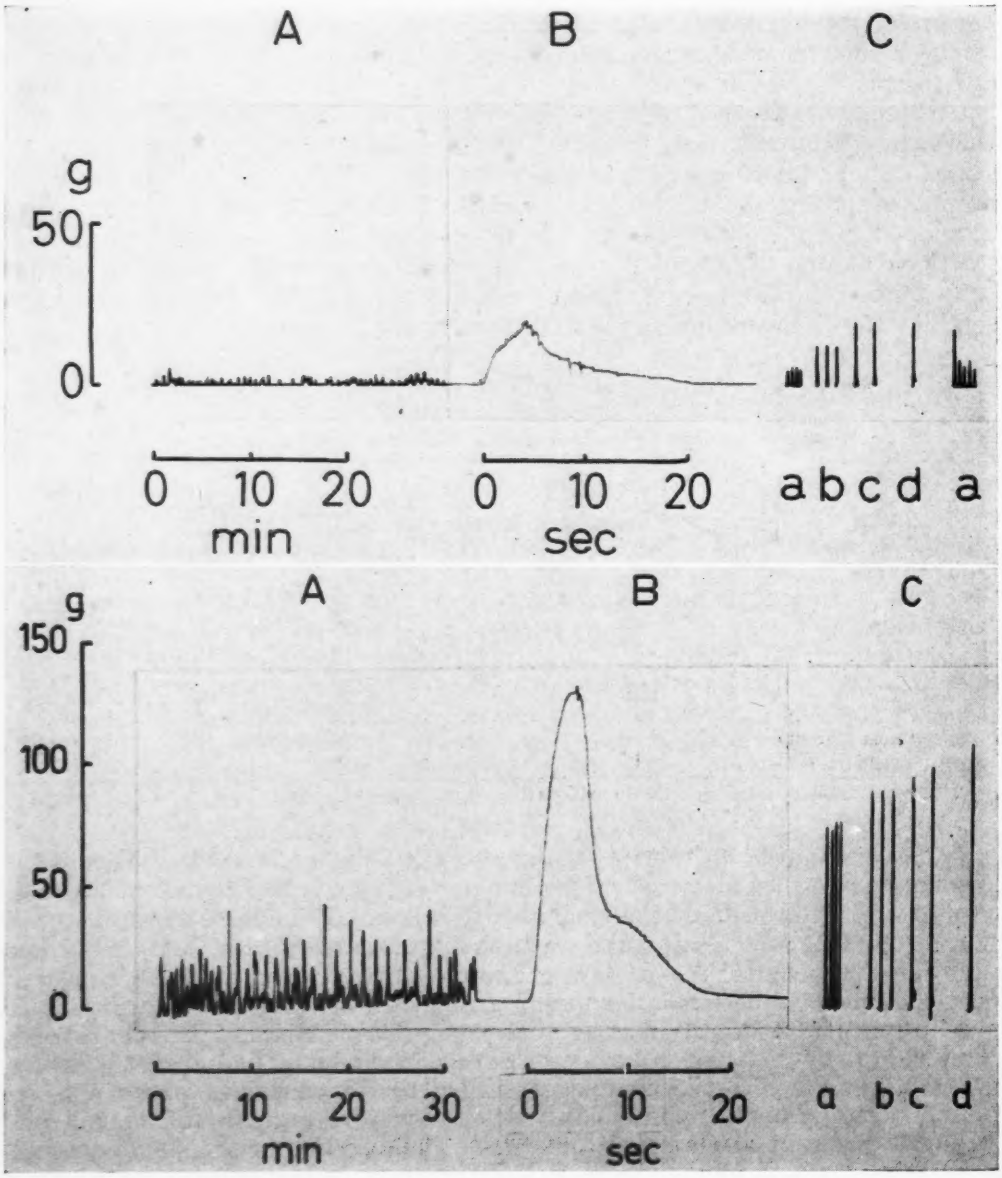

Fig. 5.

Fig. 4.—Record from a six days pregnant uterus. *A*, Spontaneous contractions. *B*, Single contraction curve after electrical stimulation (about 5 volts per centimeter, 5 seconds' duration, 60 cycles per second alternating current). *C*, The staircase. Electrical stimulation as in *B*. Repetition frequency in *a*, 30 seconds; *b*, 1 minute; *c*, 2 minutes; and *d*, 4 minutes.

Fig. 5.—Record from a 26 days pregnant uterus. Symbols as in Fig. 4.

(55 per cent of maximum tension). The duration of the single contraction cycle has increased to 32 seconds and the staircase has become more positive than it was 12 hours before. Maximum tension also increases somewhat to a

value of 179 Gm. per gram of muscle. This increase is probably due to the complete withdrawal of progesterone block and thus to full restoration of conduction. This value represents the maximum working capacity of the postpartum myometrium and is very similar to the value which can be obtained in vitro by stimulation in a uniform electric field. The length-tension

Fig. 6.

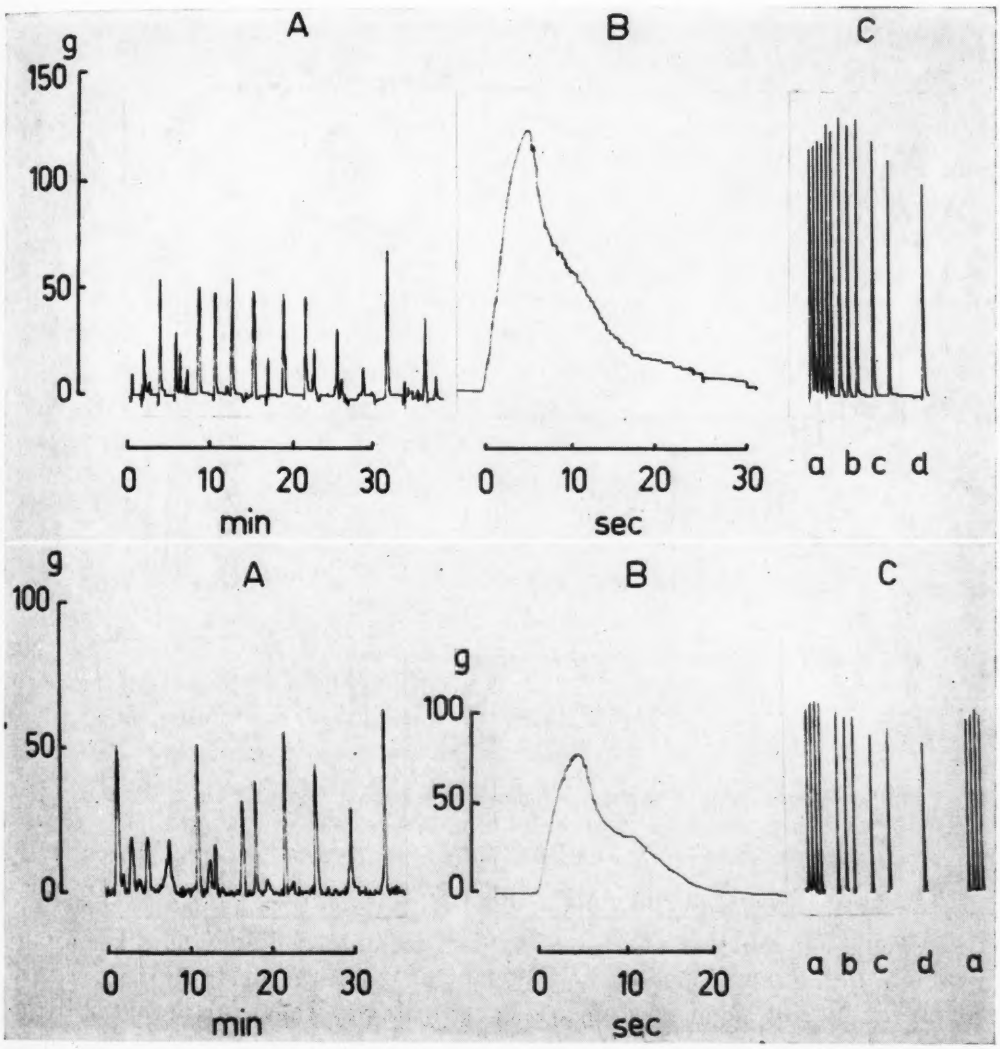

Fig. 7.

Fig. 6.—Record from a 29 days pregnant uterus. Symbols as in Fig. 4.
Fig. 7.—Record from a uterus some hours before parturition. Symbols as in Fig. 4.

diagram in this condition, moreover, has been found to be similar to that of the estrogen-dominated nonpregnant animal.[7] It appears therefore that 12 hours post partum the functional behavior of the uterus is similar to that of an animal in natural estrus, or an ovariectomized animal treated with estrogen. Only maximum tension is larger; this can be accounted for by the increased actomyosin content under this condition.[4]

At 24 hours post partum, the myometrium exhibits the same behavior as at 12 hours post partum except that the duration of the single contraction

cycle is still longer (36 seconds) and that spontaneous isometric contractions amount to only 40 per cent of maximum tension. It is also significant that maximum tension begins to drop. The concentration of actomyosin[4] was also found to decline at this time.

As compared to the myometrium 24 hours post partum, the only significant change 48 hours after delivery appears to be a further drop in maximum tension to a value of 90 Gm. per gram of muscle.

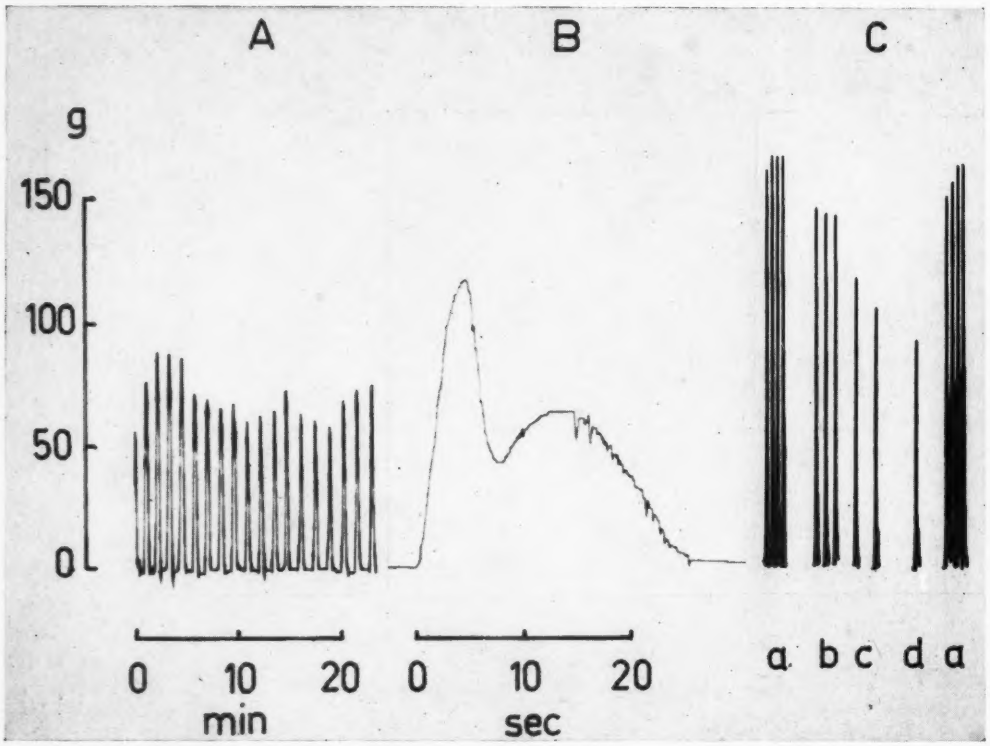

Fig. 8.—Record from a uterus 12 hours post partum. Symbols as in Fig. 4.

Summary

The present experiments clarify the following points:

1. Provided that extreme care is taken to maintain light anesthesia, undisturbed breathing, constant body temperature, and constant temperature around the uterine segment from which recording is made, furthermore, if the tension is recorded isometrically, there is no significant difference between in vitro and in vivo findings. This suggests that the reactivity of the myometrium is determined by the endocrine state of the animal and that other mechanisms working in the body are of lesser importance.

2. That the method here employed is satisfactory has been established in several different ways:

a. Between the steps of an experiment in which electrical stimulation was employed, it was always possible to observe the same pattern of spontaneous activity as found at the beginning of the experiment.

b. All animals in the same group exhibited the same pattern of uterine behavior, and even the quantitative differences from one animal to another

in the same group were slight. Among all the tests employed in these studies, spontaneous activity showed the greatest and the staircase the smallest variation.

c. When the patterns of behavior of the two horns of the uterus of one animal were compared, the similarity between the two records obtained was very close.

d. When tension was recorded continuously for a period of 5 hours in an estrogen-treated nonpregnant rabbit, the uterus being stimulated electrically with optimum stimulus once every 4 minutes, tension remained unchanged. This, we believe, is one of the most convincing tests of the reliability of the technique and the unchanged condition of the animal during the experiment.

3. These experiments demonstrate that until the twenty-ninth day of pregnancy progesterone dominates the myometrium. The effect of progesterone begins to decline only on the twenty-ninth day, its withdrawal being completed on the thirty-second day, the day on which labor occurs.

4. A few hours before delivery, on the thirty-second day, the myometrium is clearly estrogen dominated. Its excitability is optimal. Its conductivity appears to be restored, its intrinsic stimulatory system is highly efficient, and development of spontaneous tension is at its best. Working capacity is maximal. It appears, therefore, that all conditions are optimal as required for maximum function, and the uterus is ready to perform its main physiological function, i.e., the delivery of the conceptuses.

5. Shortly after delivery estrogen domination approaches an extreme condition so far as excitability of the myometrium is concerned, whereas working capacity begins to decline, and 48 hours after delivery it is similar to the value which can be obtained in the nonpregnant estrogen-dominated animal.

It is to be hoped that the findings and methods reported in this paper will be useful in devising means by which studies on the human myometrium can be carried out in order to establish changes in endocrine domination in women during normal and abnormal pregnancies.

This work was supported by the Swedish Medical Research Council, The Rockefeller Foundation, and Lunds Läkarsällskap. I am grateful to Dr. George W. Corner for the hospitality of his laboratory and to Dr. Arpad Csapo for his valuable help in designing and carrying through these experiments.

References

1. Corner, G. W.: The Hormones in Human Reproduction, Princeton, 1942, Princeton University Press.
2. Corner, G. W., and Csapo, A.: Brit. M. J. 1: 687, 1953.
3. Csapo, A.: Am. J. Physiol. 177: 348, 1954.
4. Csapo, A.: The Mechanism of Myometrial Function and Its Disorders, in: Bowes, Kenneth, editor: Modern Trends in Obstetrics and Gynecology, London, 1955, Butterworth & Co., Ltd., pp. 20-49.
5. Csapo, A.: Am. J. Anat. 98: 273, 1956.
6. Csapo, A.: J. Physiol. 133: 145, 1956.
7. Csapo, A., and Goodall, M.: J. Physiol. 126: 384, 1954.
8. Schofield, B. M.: Endocrinology 55: 142, 1954.
9. Schofield, B. M.: J. Physiol. 129: 289, 1955.
10. Reynolds, S. R. M.: Physiology of the Uterus, ed. 2, New York, 1949, Paul B. Hoeber, Inc.

MEASUREMENT OF THE MIDPELVIS WITH THE RECTOVAGINAL PELVIMETER TO MINIMIZE EXPOSURE TO RADIATION

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THE public is becoming increasingly conscious of, and concerned over, the genetic hazards of exposure to ionizing radiation. This is not surprising, in view of the rapid developments in nuclear physics, and the promise of their application in daily life, as well as in weapons of war. It is, therefore, time for the physician, and particularly for the obstetrician, to reappraise the risks of induced mutations due to diagnostic x-ray procedures, especially pelvimetry.

There are some objections to x-ray pelvimetry, namely, the cost, unavailability of apparatus or personnel, and a theoretical danger to the fetus.[1, 2] The unrestrained enthusiasm of recent years for x-ray pelvimetry should, therefore, be curbed, if alternative methods can be substituted.

Satisfactory alternative clinical methods have long been available, at least in so far as the lower part of the pelvis is concerned. A rectovaginal pelvimeter for the measurement of the midpelvis and of the pelvic outlet was devised over two decades ago.[3] With the use of this pelvimeter, it is possible to limit x-ray pelvimetry to only one exposure, to show the contour and size of the pelvic inlet, and the need for even this one exposure is reduced. A revival of interest in this long-neglected and half-forgotten instrument is, therefore, recommended.

The instrument (Figs. 1 and 2) consists of a vaginal blade (*V*), and a rectal blade (*R*), which are detachable. There is a ring at the end of each blade, by means of which it is possible to guide the ends of the instrument to the tips of the ischial spines, or other end points, the distance between which is to be measured. A scale, graduated in centimeters, to represent the distance between the rings, is attached to the opposite end of one of the blades. The instrument, and especially its rings, should properly fit the examiner's hand. It should, therefore, be made available in at least three sizes—small, medium, and large. The instrument shown here is of medium size.

The procedure of applying the instrument for the measurement of the transverse diameters of the midpelvis is as follows:

The blades of the pelvimeter are separated. The tip of the middle finger of the right hand is inserted into the ring of the vaginal blade. With the blade in place resting on the dorsum of the hand, the index and middle fingers are introduced into the vagina. The tip of the index finger of the left hand is similarly placed within the ring of the rectal blade, and is introduced into the rectum. The two blades are now joined and held together by means of a screw, which is put on and tightened by an assistant. The ischial spines are identified, one at a time. The rings are then steadied against the tips of both spinous processes simultaneously, and a reading is made quickly on the scale. The midplane bi-ischial diameter[4] is measured similarly, with the exception that the rings are carried anteriorly to the bases of the ischial spines when the reading is taken.[3]

The anteroposterior diameters of the midpelvis and of the pelvic outlet, including the anterior and posterior sagittal diameters, can be measured with the same instrument by merely reversing the vaginal blade (Fig. 3), and by applying the instrument in the manner previously described.

The only objection to the use of the rectovaginal pelvimeter for the measurement of the bispinous diameter[3] is the supposed painfulness of the procedure. With a little practice, however, at first on multiparas in whom the perineum is relaxed, the necessary dexterity can be readily acquired so that measurements can be taken accurately in a "split second," causing only slight and fleeting pain. This is especially true if the procedure is carried out late in pregnancy, preferably during the seventh month, or even in the eighth month, provided, of course, that aseptic precautions are observed. This statement is based, not on hearsay, but on a personal experience of measurements taken in over 10,000 cases; it cannot, therefore, be regarded as an untried procedure. Torpin[5] also has had considerable experience in the use of the instrument, and found it entirely suitable for the purpose recommended.

Fig. 1.—The rectovaginal pelvimeter. Frontal view. Rectal blade (*R*). Vaginal blade (*V*). (One-fourth actual size.)

The statement often seen in the literature, that the midpelvis can be measured only by x-ray is consequently out of conformity with the facts, and is misleading. On the contrary, the clinical measurements, being simple and

direct, are more reliable and more accurate than those obtained from x-ray films, which are subject to error because of faulty positioning of the patient, poor visualization of the end points, or errors in calculation of results. The chief reason, however, for the reintroduction of the rectovaginal pelvimeter is the limitation of x-ray pelvimetry to only one exposure, or even the total avoidance of radiation which it makes possible, and the consequent reduction or elimination of the risk of genetic damage.

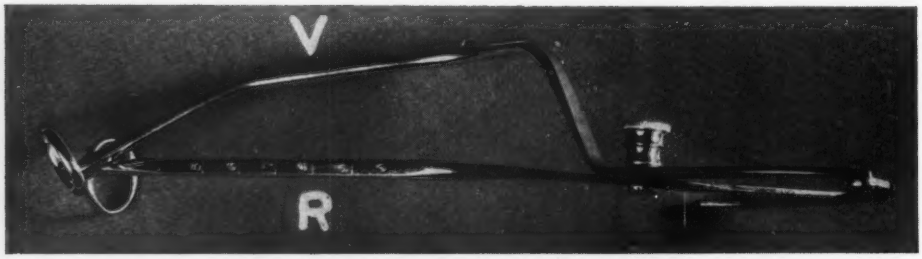

Fig. 2.—The rectovaginal pelvimeter. Lateral view. Rectal blade (*R*). Vaginal blade (*V*). (One-fourth actual size.)

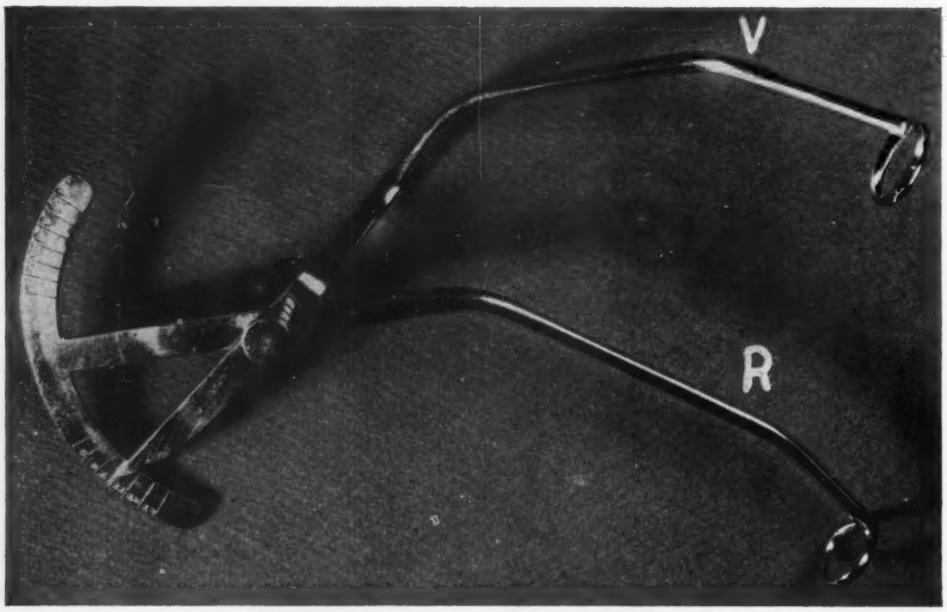

Fig. 3.—The rectovaginal pelvimeter. Vaginal blade (*V*) reversed, for the measurement of the anteroposterior diameters. (One-fourth actual size.)

Summary

A rectovaginal pelvimeter, first devised over two decades ago, is reintroduced. By means of this instrument, all of the diameters of the midpelvis can be measured readily and accurately. X-ray pelvimetry can consequently be reduced to only one exposure, and even this one exposure can often be avoided. The hazard of genetic damage from exposure of the gonads to radiation can thus be minimized.

References

1. Committee Report, Medical Research Council, The Hazards to Man of Nuclear and Allied Radiations, London, 1956, Her Majesty's Stationery Office.
2. Muller, H. J.: Scope Weekly (Upjohn Co., Kalamazoo, Michigan) **1**: 1, 1956; also personal communication.
3. Hanson, Samuel: AM. J. OBST. & GYNEC. **35**: 228, 1938.
4. Hanson, Samuel: AM. J. OBST. & GYNEC. **64**: 1374, 1952.
5. Torpin, R.: A Treatise on Obstetric Labor, Augusta, Ga., 1948, Augusta Obstetrical and Gynecological Book Co., pp. 23-56, 187-188, 533-546.

1001 WEST VINE STREET

A NEW ADJUNCT TO ANALGESIA AND SEDATION IN LABOR

Preliminary Report of Results With Promazine Hydrochloride by Intravenous Injection

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ANALGESIA and sedation are acknowledged requisites to the management of labor. Despite years of research and clinical trial, however, there is still no agreement as to the most suitable measures for the purpose. As yet, no method has been reported that will adequately fulfill all eight criteria for pain relief during parturition: (1) no respiratory or cardiovascular depression in the infant; (2) no deleterious effect (as circulatory, respiratory, or central nervous system disturbance) in the mother; (3) adequate alleviation of emotional tension and obtundation of pain; (4) no interference with the normal mechanism of labor; (5) no incompatibility with accepted anesthetics or other agents required during labor and delivery; (6) retention by the patient of sufficient command of her mental faculties to permit satisfactory response to instructions; (7) rapidity of action; (8) ease of administration.

With the advent of the so-called "tranquilizers," obstetricians looked with new hope for the long-awaited agent that would provide the desired neuromuscular relaxation, and that could be safely administered by vein for rapid and definite response. Attention was directed to the phenothiazine series in particular, because of the reputed[1, 2] potentiating effect of the various compounds in the group on the commonly used hypnotics and analgesics.

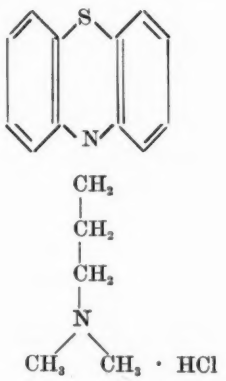
Chlorpromazine, which is obtained by addition of a dimethyl amino n-propyl group to the phenothiazine nucleus, and a chlorine atom in the second position (Fig. 1), is known to have a pronounced depressive action on the central nervous system, particularly the central autonomic functions. Reports of the performance of chlorpromazine in sedation and analgesia during labor are now numerous.[3-7] Many of these reports have appeared in the European literature, and have been reviewed more extensively elsewhere.[8] The American literature on this subject has been well analyzed by Anz and Smith.[4] These authors describe a diversity of experiences and express varying degrees of disappointment with the results obtained. For intravenous use in labor, the compound has been avoided because of the risk of precipitous fall in blood pressure and other toxic side effects.

We continued to search for improved modifications of phenothiazine, the parent compound, and were led to try promethazine, a substance with strong

antihistaminic and sedative properties, formed by addition of a dimethyl amino-isopropyl group to the phenothiazine nucleus. Our interest was then attracted to the similarity between the chemical composition of chlorpromazine and promazine.* In both the molecular structure is the same—the side chain is $—CH_2—CH_2—CH_2—N^R_R$ but promazine lacks the chlorine atom (Fig. 1).

The singular somnifacient action shared by both promazine and promethazine has been described by Decourt[9] as narcobiosis, and later alluded to as "psychic sedation" by Holzmann.[10] By virtue of such activity, the fundamental metabolic functions of the brain cells, particularly in nervous tissue of reticular type, are inhibited. The alteration in subcortical function, with blocking of encephalic activity and the vomiting center, is to be distinguished from true narcotic action, which is believed to correspond to simple activity on the physical structure of the cells, mainly in the cortex. Thus the intensity of the response to abnormal stimuli is reduced without depression of the mental faculties.[9] An agent, the properties of which combine lessening of emotional sensibilities to pain and tension with a neuromuscular relaxant action influencing the cervix and lower uterine segment, would approach the ideal for use during labor and delivery.

Promazine Hydrochloride
(gamma-dimethylamino-propyl phenothiazine)



Chlorpromazine Hydrochloride

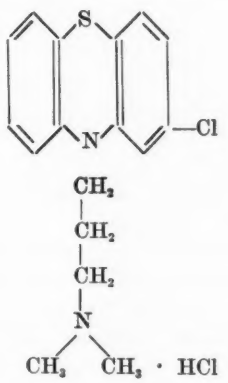


Fig. 1.

Procedure

Labor was conducted in 100 consecutive patients (approximately 80 per cent of whom were private patients), with the use of promazine as an adjunct to analgesia and anesthesia. There was no apparent bleeding and no disproportion present in this series. No radical differences were detectable in the behavior of the patients; however, those (especially of Latin extraction) seen in the clinic were inclined to be somewhat more apprehensive. In general, the clinic patient, who has received all her prenatal care under a series of physicians and is perhaps delivered by one she has not seen before, approaches labor in less satisfactory rapport with the obstetrician than does the private patient who is attended by the same physician who has treated her throughout pregnancy.

*Sparine hydrochloride, Wyeth Laboratories.

Sixty-eight had borne one or more children. Gravidity ranged from i to xv and parity from 0 to xii. All deliveries in this series were at term.

Nine patients were mildly toxemic, with systolic pressures ranging from 150 to 160 mm. Hg before the onset of labor.

An attempt at grading the emotional state of the patients prior to receiving promazine is shown in Table I.

Half of the patients had ruptured membranes at the time promazine was administered. An analysis of these factors and the relationship of administration of the medication to the state of labor also are included in Table I.

TABLE I. PREMEDICATION WITH PROMAZINE AS AN ADJUNCT TO THE MANAGEMENT OF LABOR IN 100 CASES

Emotional Condition Before Medication.—	
Severe emotional tension*	54
Moderate apprehension†	35
Mild anxiety‡	11
Time of Medication After Onset of Labor.—	
Less than 1 to 1¾ hours	21
2 to 4½ hours	38
5 to 9½	36
12 to 16 hours	5
Regular Contractions at Time of Medication.—	
Strong (3 to 5 minutes)	76
Moderate (3 to 5 minutes, a few 10 to 15 minutes)	21
Mild (3 to 15 minutes)	3
Cervical Dilatation at Time of Medication.—	
2 to 4 cm.	25
5 to 7 cm.	73
8 cm.	2

*Trembling, crying; some uncooperative, throwing themselves about, loudly asking for something with almost every contraction.

†Moaning and sighing between contractions; crying, restless, and asking for something with most contractions.

‡Fairly quiet but evidently apprehensive; turning about with contractions.

Dose.—In every case, *one injection of 50 mg.* promazine was administered intravenously, on admission, if the patient arrived in active labor, or as soon afterward as regular contractions were definitely established.

Additional medication was administered at the discretion of the attending physician. The data concerning the predelivery medications used in this series may be seen in Table II.

TABLE II. SEDATIVE-ANALGESIC ADJUNCTIVE MEDICATION WITH PROMAZINE IN 100 CASES

MEDICATION	PATIENTS (%)
Sedatives, analgesics, or amnesics, 1 dose 3 to 9 hours before promazine, no other medication	5
Promazine only	16
50 mg. meperidine with or after promazine	45*
100 mg. meperidine after promazine	2
50 mg. meperidine with promazine, 1/150 grain atropine in delivery room	3
1/150-1/100 grain atropine only, after promazine	29
Total	100

*Two patients received 1/200 grain scopolamine with the meperidine.

Sixteen patients received no other predelivery medication, 48 received one dose of 50 mg. meperidine with or after the dose of promazine; and 32 received 1/150 or 1/100 grain atropine for the drying effect. Two patients received

1/200 grain scopolamine in addition to the analgesic medication. Only 2 patients received a second dose of meperidine (total dosage 100 mg.) after the injection of promazine. This represents an average dose of 26 mg. meperidine per patient for the entire series.

Blood Pressure.—A resident physician remained with the patient continuously from the time promazine was administered until two hours after delivery. Throughout this period the patient's blood pressure and the fetal heart rate were determined every five minutes. Thus any significant change in either would have been detected immediately.

Results

The response to intravenous injection of promazine was graded as: (1) excellent, (2) good, (3) fair. Seventy per cent had an excellent result. Regardless of the anxiety they exhibited before medication, these patients immediately became quiet and relaxed. Some slept soundly without being completely aroused by contractions, and had little or no memory of labor and delivery. Others dozed between contractions, and occasionally sighed or moaned and turned on the side during pains. This group included all the 32 primiparas, each of whom received promazine forty-five minutes to about four hours after the onset of regular contractions, and the patients who received scopolamine in addition to the injection of promazine. On being questioned the next day most reported that the pain lessened immediately after the injection and that they remembered very little afterward. The patients who had received scopolamine reported a vague memory of labor but little or no recollection of the delivery room.

Twenty-five per cent had good results. These patients immediately became relaxed and slept between the contractions, which usually partially awakened them. Some sighed, moaned, or turned about with contractions. They had a somewhat clearer memory of labor, but usually little of the delivery room. On being questioned on the first postpartum day they usually replied that the pain became less intense after the injection, and that although they were aware of some of the contractions they were "too sleepy to mind." It was noted that the medication was administered to this group (none of whom received scopolamine) somewhat later in labor than was the dose given to the patients in whom results were excellent.

In 5 per cent the result was considered fair. All these patients were the multiparas in whom delivery occurred in an average of one hour or less after the injection. It seemed obvious that in these patients there was insufficient time to achieve the full measure of relaxation afforded by the medication.

The time between administration of the medication and delivery was remarkably short. Of the primiparas, 41 per cent were delivered in less than 2½ hours after medication, 47 per cent in 4½ hours, and the remaining 12 per cent in 6 to 7½ hours after medication.

Of the multiparas, 73 per cent were delivered in less than 1¾ hours after the medication was given, 20 per cent in 2 to 5 hours, and 7 per cent in 6½ to 7½ hours after the medication.

The duration of labor after the administration of promazine appeared to be shorter than might ordinarily have been expected. In the entire series delivery occurred in an average of 3 hours after the injection, with a range of less than one to 7½ hours.

Total Duration of Labor.—Among the primiparas, total labor was 3 to 6¾ hours in 44 per cent; 7 to 10½ hours in 35 per cent; and in 21 per cent was 11 to 17 hours.

Total labor among the multiparas was one to 2½ hours in 15 per cent; 3 to 7½ hours in 62 per cent; and 8 to 10¾ hours in 16 per cent. The multiparas in whom labor lasted more than 12 hours (7 per cent) had been in labor 9 to 13 hours, with dilatation of 2 to 6 cm., when promazine was first administered.

There seemed to be a direct relationship between the length of labor or the cervical dilatation achieved before administration of promazine and the degree of relaxation obtained by this adjunctive medication. Best results were obtained in patients who received medication early in labor, preferably at a cervical dilatation of 2 to 6 cm. If cervical dilatation exceeded 6 cm., there was usually insufficient time before delivery to attain the desired response.

Delivery.—Normal spontaneous delivery occurred in 71 per cent of the entire series; low forceps were used in 22 per cent. Of the remaining 7 cases there was one assisted breech delivery, one Kielland rotation and forceps delivery, and 5 low midforceps deliveries. Of the 32 primiparas, 60 per cent had normal spontaneous deliveries, and 22 per cent were delivered with low forceps. Sixty-eight per cent of the deliveries were performed over an elective episiotomy.

Anesthesia.—General anesthesia was used in all but one case. This patient was delivered without anesthesia. The standard gas-oxygen-ether combination was administered to 58 per cent and nitrous oxide-oxygen only to 41 per cent. No spinal anesthesia was used in this series, and no cesarean sections were performed.

The patients usually came to full consciousness very soon after delivery or repair of the episiotomy, and were able at once to notice and appreciate the presence of their babies.

Infant Weight.—The weight of the infants ranged from 6 to 9 pounds, 5 ounces, with a median of 8 pounds. This would be considered definitely larger than the so-called "average birth weight."

Blood Pressure.—In all cases the variation in blood pressure, usually to be expected during active labor, remained within normal limits. The pressure usually rose at the height of the contractions and fell, never more than 10 to 20 mm. Hg, in the intervals between. In 28 of the patients there was no change in systolic pressure whatsoever. In the 9 patients with mild pre-eclampsia, the pressure fell slightly after administration of promazine, and was normal in the recovery room after delivery.

Fetal Heart Rate.—The fetal heart rate was regular in all cases, and remained within normal limits, ranging from 122 to 160, with an average of 144.

Blood Loss.—In 98 cases the blood loss was estimated at 100 to 200 c.c., with a median of 150 c.c., which is within normal limits. Uterine atony was thought to be responsible for the unusual bleeding that occurred in 2 patients, since there was no cervical laceration or retention of placental tissue in either. The estimated blood loss was 1,000 c.c. in one, a primipara who received the injection of promazine at 4 cm. dilatation, and was delivered by midforceps 3 hours later, after a total labor of 6¾ hours. The other patient, a multipara, received the injection at 5 cm. dilatation, and assisted breech delivery was performed one hour later, after a total labor of 3¾ hours. The estimated blood loss in this case was 500 c.c.

Fetal Depression.—No infant showed depression, none required even minimal resuscitation or stimulation, and all had a good pink color on delivery. All breathed and cried spontaneously immediately after birth. With labor conducted under conventional sedation and analgesia, or with none at all, stimulation and resuscitation of the infant are often necessary.

One infant became slightly cyanosed shortly after delivery, and on examination was found to have a cleft palate.

Patient Response.—There was no nausea or vomiting during labor and delivery, and there was less postpartum emesis than is usually seen after a general anesthetic.

No patient showed disorientation or hyperactivity during uterine contractions, so undesirable but commonly seen with barbiturate sedation and scopolamine amnesia. All were able to respond appropriately to questions and instructions during labor, although they had little memory of such conversations afterward. No confusion or excitement occurred in the postpartum period.

Comment

Barbiturates were eliminated from the predelivery medication in this series, and significantly less of the analgesics was required. The amount of meperidine administered per patient is believed to be the lowest yet reported. There was a considerable improvement in the atmosphere of the labor room, and there were fewer demands on the nursing staff than is usually the case during labor under conventional management.

Delivery in all cases was accomplished under lighter, more transient anesthesia than is usually practicable. Episiotomy and low forceps delivery, particularly in the primiparas, could be performed with greater frequency under nitrous oxide-oxygen alone. The 2 per cent incidence of early postpartum hemorrhage compares favorably with the usual over-all incidence of 5 per cent.

Promazine may in some way exert a relaxant effect on the lower uterine segment and cervix. Possibly the release of physical tension in the cervical region is a corollary to the general alleviation of emotional stress and fear in the patient.

Larger doses may perhaps be an eventuality. It is our feeling that when promazine is combined with a small dose of scopolamine the amnesic effect is considerably enhanced. Further study of this method of medication is recommended.

Some method should be developed for objective determination of the onset, degree, and duration of action of the compound, as a complement to observation and evaluation of the subjective effects in the patient. The pupillary response after administration of the dose, in our experience, is extremely variable and bears no direct relationship to the clinical results.

Apparently, what Read[11-13] tried to do, that is, to eliminate fear and anxiety by psychoprophylaxis, and achieve voluntary muscular relaxation by a regimen of exercises, has been accomplished satisfactorily in practically all cases, and with safety to both mother and child, by one intravenous dose of a chemical compound, promazine hydrochloride.

Summary and Conclusions

One hundred patients, in labor at term, received one injection of 50 mg. promazine intravenously when regular contractions were established. The average dose of meperidine required was 26 mg. per patient for the entire series.

The emotional and physical relaxation obtained was excellent in 70 per cent, good in 25 per cent, and fair in 5 per cent.

The duration of labor after medication appeared to be shortened, with no adverse effects on the mothers or infants.

The earlier in active labor the medication was administered, the more satisfactory the response. If, at administration of the dose, dilatation of the cervix had progressed to more than 6 cm., there was insufficient time for development of the maximum sedative effect. This was the case in the 5 per cent of the cases in which results were considered fair.

Promazine hydrochloride, administered by vein, appears to satisfy all the criteria established for adjunctive medication in obstetrics, and is considered preferable to other measures.

References

1. Editorial: New England J. Med. 252: 74, 1955.
2. Harrison, G.: Brit. J. Anaesth. 27: 131, 1955.
3. Hershenson, B. B., et al.: New England J. Med. 251: 216, 1954.
4. Anz, U. E., and Smith, L. J.: Am. J. Obst. & Gynec. 71: 1242, 1956.
5. Schaffer, A. L.: Am. J. Obst. & Gynec. 71: 1247, 1956.
6. Norton, H. I., Weingarten, M., and McDonough, E. T.: Am. J. Obst. & Gynec. 71: 1251, 1956.
7. Harer, W. B.: Obst. & Gynec. 8: 1, 1956.
8. Albert, S. N., et al.: Anesth. & Analg. 35: 101, 1956.
9. Decourt, P.: Anesthesia 10: 221, 1955.
10. Holzmann, L., and Josipowicz, A.: Am. Pract. & Digest Treat. 7: 939, 1956.
11. Read, G. D.: Natural Childbirth, London, 1933, William Heinemann, Ltd.
12. Read, G. D.: Childbirth Without Fear, New York, 1944, Harper & Brothers.
13. Read, G. D.: Introduction to Motherhood, London, 1950, William Heinemann, Ltd.

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PLACENTAL TRANSMISSION OF VIRUSES*†

With Especial Reference to the Intrauterine Origin of Cytomegalic Inclusion Body Disease

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CYTOMEGALIC inclusion body disease is a condition produced by a virus which is extremely widespread among animals and humans but which is rarely responsible for pathologic changes. When it is placentally transmitted to the fetus, however, it may cause a fatal disease. Information concerning this virus and the effects it produces has gradually been accumulating for the past fifty years and now the picture is fairly complete.

That embryonic tissues are more susceptible than adult tissues to virus infections has long been recognized and put to practical use in the identification and propagation of viruses. Many viruses can be cultivated successfully in tissue culture and many will grow in chick embryos that produce no response in young or adult fowl. In some instances, young embryos of 5 to 6 days rapidly develop evidence of generalized infection following inoculation, while those of 18 to 20 days show no spread.[1] Guinea pigs can be inoculated in utero with vaccinia virus or the guinea pig strain of salivary gland virus and will succumb to the infection, while injection of similar amounts in adult guinea pigs will produce no symptoms.[2] The natural transmission of a virus infection to the fetus in utero from a symptomless mother has been described in virus abortion in mares[3] and to the suckling young of hamsters in West Nile and Semliki Forest virus.[4] Vaccination of sows with modified live hog cholera virus (for purposes of immunization) 10 to 16 days after breeding results in a high fetal loss; almost half the offspring have been reported as stillborn, while most of the others have developed fatal ascites or generalized edema. Virus sufficiently virulent to cause death in susceptible 12-day-old guinea pigs has been isolated from the fetal spleens.[5] Similar transmission to fetuses of blue tongue virus has been described following vaccination of ewes 4 to 8 weeks pregnant with modified live virus vaccine.[6] The fetuses born dead have a brain malformation similar to human hydranencephaly; those which survive birth are usually "dummies" and are often dumb or blind.

Mice infected with a human strain of influenza virus have been shown to have a decreased pregnancy rate and an increase in fetal malformations.[7]

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Susceptible mares will abort following natural exposure to the agent responsible for mare virus abortion as well as following experimental inoculation of raw or filtered material from aborted fetuses.[3] Vaccination of humans against smallpox during pregnancy has been reported to have no effect on the fetus.[7a]

The possibility of transmission in the human of viral infections from mother to fetus has also been long known and in the early part of the century cases were described in which fetuses were born with evidence of healed smallpox lesions as well as in the eruptive stage of the disease.[8] The older literature contains many reports in which the eruption of measles was described at the time of birth and Dyer[9] more recently reported 3 cases of intrauterine transmission. At our hospital the vesicles of chicken pox were observed to develop in an infant 3 days of age, and Shuman[10] reported the case of an infant with vesicles at 2 days of age. Poliomyelitis seems ordinarily not to affect the fetus in utero although one group of 30 women with the disease in the first trimester had a fetal loss of 46 per cent.[11] At least one case has been reported in which the disease developed so soon after birth that intrauterine transmission seems almost a certainty.[12] The Australian epidemics of rubella established the serious nature of the effect on the fetus of maternal infection by this virus during the first trimester.[13, 14] In this condition, however, it has not been known whether the fetus actually contracts the disease and recovers or whether the abnormalities of development that may be present at birth are indirectly produced as a result of alterations in the environment during the course of the maternal disease.

That certain viruses may affect the very young infant and produce characteristic lesions is also established and the number of such viral infections to be recognized is slowly being augmented. Inclusion blennorrhea is a conjunctivitis appearing 5 to 7 days after birth, believed to be contracted during delivery from a symptomless viral infection of the cervix of the mother.[15] The virus of herpes simplex has been isolated from the liver of one newborn infant and nuclear inclusions have been observed in others in association with symptoms of cyanosis, icterus, vomiting, fever, respiratory distress, and circulatory collapse. The symptoms appear 5 to 7 days after birth and are thought to result from an infection contracted at the time of birth from mothers with gingival or vulvar lesions.[16] An epidemic of myocarditis caused by coxsackie group B virus was reported from a maternity home in Johannesburg with onset of symptoms 5 to 17 days after birth with 6 fatalities among 10 cases. At the same time, Bornholm disease, a nonfatal condition affecting adults, also caused by coxsackie group B virus, was prevalent in the community.[17]

The viruses listed above are, for the most part, examples of those which in a mature organism produce little or no disturbance but which in the newborn may be fatal. Other conditions thought to be viral in nature because of the presence of intranuclear inclusions but from which no viruses have been isolated have also been observed. They have especially affected the lungs. Three epidemics of pneumonia in infants a few days old have been described in Minneapolis,[18] and in other places isolated cases of pneumonia associated with intranuclear inclusions have been reported.[19]

Of most interest to the obstetrician are the viruses that can be transmitted from the mother to the fetus and in cytomegalic inclusion body disease a condition is present in which an apparently healthy mother can transmit the virus to the fetus with production in the latter of a lethal disease.

The first description of the cells now considered to be characteristic of those associated with the presence of the salivary gland virus (Fig. 1) is credited to Ribbert. He described them originally as hypertrophied cells and later as ameba or sporozoa, an idea in which most writers for the next 15 years concurred.[20] In 1910, Smith and Weidman[21] gave the name *Entamoeba mortinatalium* to these supposed organisms. The fact that syphilis was also thought to be present in many of the infants in whom this diagnosis was made led some to think these structures might be an unusual manifestation of this disease rather than protozoa. Goodpasture and Talbot[22] decided that degenerative changes converted normal cells into large cells with a prominent mass in the nucleus and coined the term cytomegalia for cells showing such changes.

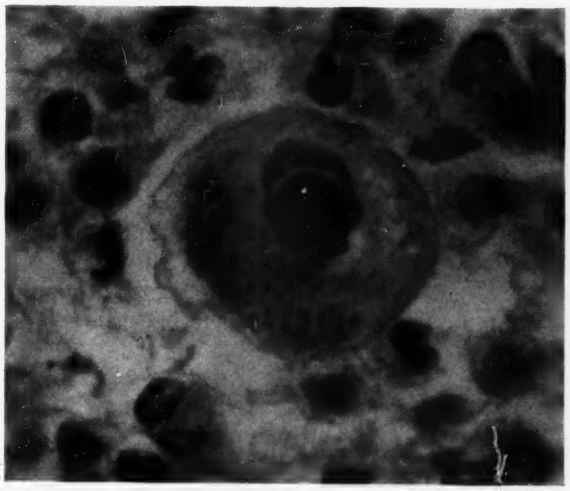

Fig. 1.—Cell free in alveolus showing typical intranuclear and intracytoplasmic inclusions. Note large size of cell.

In 1922, Jackson[23] described as protozoan parasites similar cells in the salivary glands of guinea pigs. Evidence began accumulating about that time that certain types of intranuclear and intracytoplasmic bodies were associated with virus infections and before long the viral nature of the condition responsible for these lesions observed in guinea pigs was established by transmitting the disturbance from one guinea pig to another.[24] The responsible agent was designated the salivary gland virus.

Inclusion bodies in salivary glands characteristic of those produced by the salivary gland virus have been observed in different parts of the world in high percentages of many laboratory animals, including guinea pigs, hamsters, mice, rats, and monkeys. They have also been found in moles, and Kuttner and Wang[25] found them in 50 per cent of wild rats in Peiping. It has been possible to produce a meningitis, sometimes fatal, in guinea pigs, mice, hamsters, and rats, by intracerebral injection of virus specific for the species.[25] Smith[26] was able to produce visceral lesions in young mice by the intraperitoneal injection of material from adult mouse salivary glands. Markham[27] observed that spontaneously occurring inclusions were rare in guinea pigs less than 1 month of age but that subsequently they were present with constantly increasing frequency. Following subcutaneous, intraperitoneal,

or intravenous injection of infective gland emulsion into young guinea pigs, lesions could be demonstrated in the salivary glands within 10 to 15 days. Following intracerebral inoculations, death from meningitis occurred in 5 to 8 days when the doses were large, but produced only symptomless changes in salivary glands when doses were reduced. Markham and Hudson[2] demonstrated the extreme susceptibility of the fetus to the virus and found that direct inoculation of guinea pigs fetuses in utero was followed by a generalized response and death when doses were used that would produce not even an elevation of temperature in adult animals.

In 1932, Farber and Wolbach[28] reported finding large cells containing intracytoplasmic and intranuclear inclusions in 12 per cent of 183 postmortem examinations on children under 17 months of age. They also described 2 infants aged 2 and 20 days with similar cells in other organs. They were able to find 25 cases previously reported which had the same type of cells in salivary glands, lungs, or kidneys. They commented that although these cells might possibly indicate the existence of a disease caused by a virus no distinctive clinical or pathologic features were associated which would permit its recognition on the ward or in the pathology laboratory.

In 1936, McCordock and Smith,[29] after producing visceral lesions in mice with mouse salivary gland virus, suggested that the salivary gland virus, although possessing a low natural pathogenicity, might become generalized in especially susceptible strains or individuals. One of the objections to salivary gland virus as the etiological agent in the generalized disease in humans was based on the fact that when the cells were found in other organs they were rarely described in salivary glands. McCordock and Smith concluded that this was due in part to failure to examine salivary glands in human autopsies and also to the fact that, since in their experiments changes in salivary glands appeared later and were found only after a period of time which exceeded the survival time of severely affected guinea pigs, the same was probably true in the human.

With the report by Margaret Smith[30] in April, 1956, of the successful propagation of human salivary gland virus in tissue culture, the last doubt was dispelled that these inclusions in the human are caused by a virus which, like salivary gland viruses found in other animals, is species specific.

In the 25 years that have elapsed since the report by Farber and Wolbach, in which they described 2 cases of generalized inclusion body disease and collected 25 cases from the literature, the number of additional cases reported has not been greatly increased. A few of the recent cases have been in children several months old, although most have been in newborn or stillborn infants and a very few have been in adults. It is now evident that pathologic manifestations vary primarily in relation to age at the time of infection. Until 1952, the diagnosis had been made only at autopsy but several cases have now been observed in which the diagnosis has been established during life by the finding of desquamated renal tubule cells with nuclear or cytoplasmic inclusions in the urine.[31-34]

Infection with salivary gland virus takes 4 forms: (1) infection of adults with absence of symptoms and probably the limitation of pathologic changes to salivary glands; (2) infection of children or adults with spread to lung or intestine in the presence of debilitating disease from other causes; (3) infection in infancy or early childhood with involvement of lungs or intestine, with death from either the virus infection or associated disease; (4) infection of the fetus with production of a generalized highly fatal disease.

Until recently, most of the reported cases have been in infants a few months old. Many of these probably resulted from postnatal infection, but it is possible that some of them may have been antenatal in origin. Margaleth[33] and Birdsong and associates[34] have reported the only cases of children in whom such a diagnosis was made soon after birth who survived more than a

few days. These cases indicate that even in the newborn period the disease is not necessarily fatal. No case has been reported in which death occurred months after the diagnosis was made, so there is no way of being certain whether the virus persists and whether the older children with cytomegalic inclusions in lungs or intestine had a more generalized form of the disease at birth or whether the demonstration of inclusions only at a later date is indicative of infection subsequent to birth. The latter is probably true since in no child with the disease has a history been presented in which symptoms of the disease were present at birth.

Except for the cases reported by Farber and Wolbach most of the early cases as well as some of the more recent[34, 39] were observed in the southern United States and almost all the material I have been privileged to see has come from Florida, Tennessee, Honolulu, and so on. Many more cases have been reported from the area around St. Louis[35-38] than from any other region and it has been suggested that this is a result of greater interest in the disease, although it may be due to a greater prevalence of the virus. However, cases have been reported more recently from several places in the northern United States,[40-44] and from Canada,[45] Germany,[46-51] France,[56] Lebanon,[52] Scotland,[53] Scandinavia,[54] as well as China,[25] Java,[55] and Venezuela.[57] Although it is possible that the virus is more ubiquitous in the south, it is by no means limited to a warm climate. It seems quite certain that there is a virus distributed fairly widely throughout the world which, when affecting adults, is generally symptomless. In individuals with some debilitating illness, it may contribute to a fatal outcome and in rare instances it seems possible that it may have been the primary cause of death.

The virus can be transmitted from an apparently healthy mother to the fetus in utero with the production of a severe and often fatal form of the disease. When the infection is intrauterine, intranuclear inclusions are present in many organs and there is a general systemic response to the virus. In many of the first cases to be reported the cytomegalia was described as occurring in association with syphilis or erythroblastosis, but it now seems evident that the extensive extramedullary erythropoiesis which led to the diagnosis of syphilis or erythroblastosis is a primary manifestation of the disease caused by the salivary gland virus.

The typical findings of the disease at birth are marked enlargement of the spleen and liver, icterus, purpura, erythroblastemia, and anemia. The jaundice appears within a few hours though the mother is generally Rh positive. At autopsy, the most outstanding features are extensive ectopic erythropoiesis and the presence in many viscera of greatly enlarged cells containing intranuclear and intracytoplasmic inclusions. Invariably involved in the congenital form of the disease are the kidneys; inclusions are almost always found also in the lungs and liver. Their identification in other areas is not so constant but they have been found at times in practically all organs. The location and extent of the ectopic erythropoiesis may be identical with that in fatal erythroblastosis. Evidence of biliary obstruction may be present even in stillborn fetuses in the form of thrombi in the bile capillaries and large amounts of pigment in hepatic cells as occurs sometimes in erythroblastosis.

A lesion almost never found in erythroblastosis which has been reported in some cases of congenital inclusion body disease is calcification of the brain. This is especially marked in the subependymal regions of the lateral ventricles and is usually associated with moderate dilatation of ventricles and poor development of the convolutions. In only one previously reported case was there severe hydrocephalus.[20]

Recently a few cases have been diagnosed during life by the finding of typical cells in the urine, and at least 2 patients with such diagnoses have survived. One child[33] had purpura and an enlarged spleen at birth with a

total bilirubin of 22 mg. per cent at 14 hours and 31 mg. per cent at 36 hours. The hemoglobin fell from 15 Gm. at birth to 7.5 Gm. on the third day. Desquamated tubule cells with typical intranuclear inclusions were recovered from every urine specimen examined for the first 4 months; when the child was seen again at 7 months, they had disappeared. At 15 months, the time at which the case was reported, the child was microcephalic and markedly retarded, but x-ray failed to disclose evidence of cerebral calcification. The other child[34] had similar but somewhat more mild symptoms and was normal when seen at 11 months.

My first direct contact with this disease occurred several years ago when slides were sent me from Florida with the request that I justify my belief that maternal immunization to A or B rarely results in a fatal form of erythroblastosis. My correspondent stated that the infant with whom he was concerned was group A, the mother O with a high anti-A titer, that the child

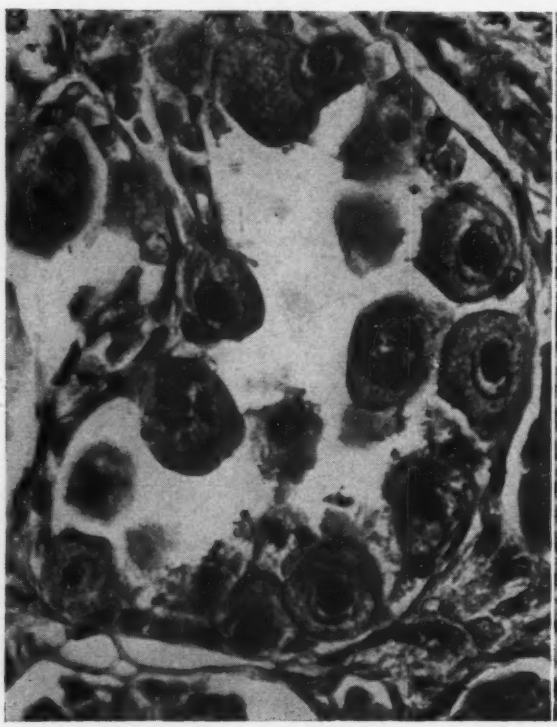

Fig. 2.

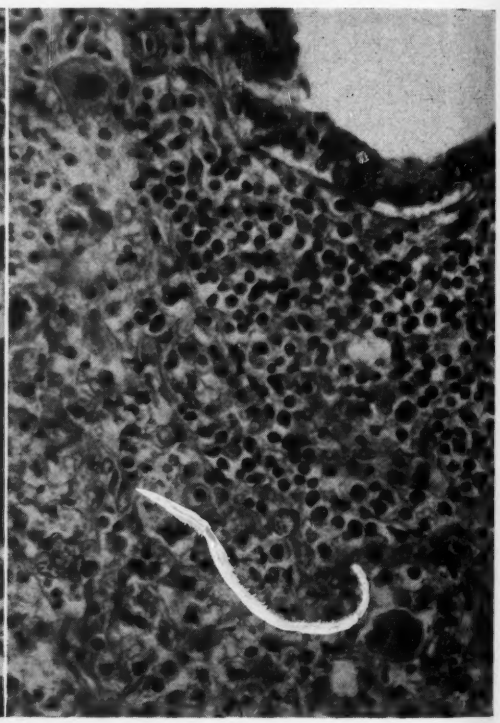

Fig. 3.

Fig. 2.—Renal tubule showing changes in many cells lining the tubule. They are greatly increased in size and the nuclei show prominent inclusion bodies.

Fig. 3.—Lung showing lymphocytic infiltration and large free cells with intranuclear inclusions.

had been born jaundiced with a great enlargement of the spleen, profound anemia, and erythroblastemia, and had died at about 24 hours of age with pulmonary hemorrhage. My correspondent thought the diagnosis was confirmed by the finding of a spleen six times the normal size with widespread ectopic erythropoiesis microscopically demonstrated. "But, incidentally," said he, "what are the large strange-looking cells in the kidneys and lungs?" It was, of course, a typical case of inclusion body disease.

The typical cells are large and prominent and I have thought them impossible to overlook. However, among 6 cases I was privileged to examine recently at the Armed Forces Institute of Pathology, received there in the last

2 years, 3 were cases that had not been diagnosed by the contributing pathologist and the typical cells had not been mentioned in the accompanying protocol.

I had not observed a case of cytomegalic inclusion disease in the course of over 8,000 autopsies on fetuses and infants that died in Chicago, in which I, myself, had made the microscopic examination of tissues. On May 18, 1954, the first infant with this condition was delivered at the Chicago Lying-in Hospital. The mother was a 27-year-old patient who had had 2 previous pregnancies, the first terminating in an abortion, the second in a normal living child. The current pregnancy was uneventful. During the course of labor, a diagnosis of hydrocephalus was established and in order to make delivery possible, 500 c.c. of fluid was removed from the head. Heart tones disappeared and the child was stillborn. Gross examination showed enlargement of the spleen (27 grams) and liver (216 grams) and extreme hydrocephalus.

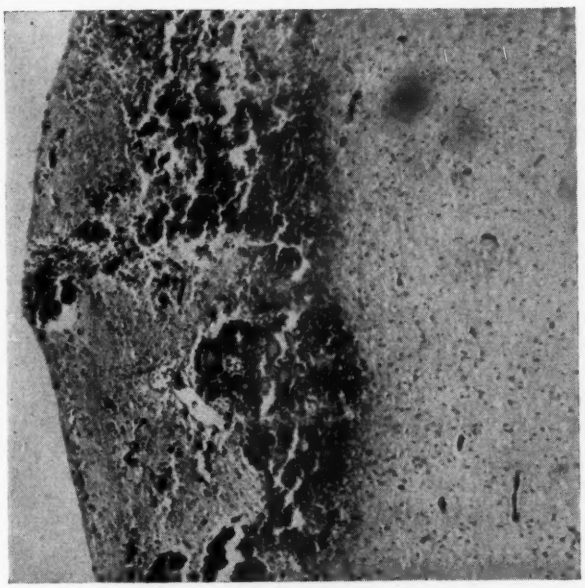

Fig. 4.—Brain showing subependymal calcification.

The cranial sutures were all approximately 4 cm. wide. The anterior and lateral portions of the cerebral hemispheres were almost paper thin with the inferior posterior portions only slightly thicker. Great dilatation of the third and fourth ventricles resulted in a hollowing out of the cerebellum.

Microscopic examination revealed widespread ectopic erythropoiesis, most marked in liver, spleen, and kidneys, similar to that observed in erythroblastosis, with cytomegalic inclusion bodies in kidneys (Fig. 2), lungs (Fig. 3), liver, and thyroid. Sections were not made of the salivary glands. The liver cells contained much hemosiderin and numerous thrombi were present in bile capillaries. The brain showed striking calcification (Fig. 4) but no inclusions could be identified.

Questioning of this patient after delivery failed to elicit any symptoms of even a minor illness during pregnancy and she had had no complaints on her prenatal visits. She continued well subsequently and in May, 1956, she was delivered again, this time of an entirely normal infant.

Conclusions

This case illustrates several important points:

1. It is possible for a woman to harbor a virus which may produce a fatal disease in her fetus without herself having any evidence of disease.

2. She may subsequently give birth to a normal infant. Whether this is because she becomes free of the virus or whether some fetuses are less susceptible and escape infection cannot be ascertained from available data.

3. When characteristic symptoms are present at birth, infection has probably occurred early in intrauterine life. The extent of the cerebral abnormality in the present case indicates that the process had been going on for at least several months.

From other cases that I have been able to study and that have been reported in the literature, it may also be concluded that:

4. Whenever a child is born with symptoms of severe erythroblastosis, the possibility that these may be caused by the salivary gland virus and not by maternal isoimmunization must be considered. This is especially true if the mother is Rh positive. When cerebral calcification is present, the disease must be differentiated from toxoplasmosis. In toxoplasmosis, however, the calcification is less extensive, is more variable in location, and generally appears later.

5. The disease, even when acquired in utero, is not necessarily fatal. The virus has a predilection for brain tissue and the child who survives may be mentally retarded. Some of the individuals now in institutions who are thought to be there because of sequelae of erythroblastosis may actually have had an infection with salivary gland virus instead.

6. The urine should be carefully examined for typical cells in any case in which the diagnosis is considered.

7. When the disease is acquired in utero cytomegalic inclusions are more prominent in the kidneys than in any other organs. When the disease is acquired in infancy and produces symptoms, inclusions are most often found in the lungs. The varying effect of this virus at different age periods is directly related to the susceptibility of the tissues at different ages. Only in the congenital form are symptoms of excessive blood destruction with compensatory erythropoiesis a prominent part of the picture. In somewhat older infants, most of the symptoms are pulmonary or intestinal. At other ages, the only evidence of the disease is ordinarily the identification of cytomegalic inclusions in the salivary glands. They may rarely be found in the viscera and then ordinarily only as an accompaniment of some debilitating disease.

Addendum.—Since the preparation of this paper an important work has been reported by Weller and associates.[58] They have succeeded in isolating a virus from living children with symptoms of cytomegalic inclusion disease. The virus in one patient came from a liver biopsy taken at the age of 3 months, in the second from a liver biopsy and from urine on 3 occasions between the fourteenth and ninety-first days, and in a third from urine in the fourth month. The latter child had been ill from birth and cytomegalic cells with inclusions had been repeatedly present from birth. The presence of the virus in the urine for a long period of time appears to be of considerable clinical importance.

References

1. Anderson, K.: Am. J. Path. **16**: 137, 1940.
2. Markham, F. S., and Hudson, N. P.: Am. J. Path. **12**: 175, 1936.
3. Dimock, W. W.: J. Am. Vet. M. A. **46**: 665, 1940.
4. Reagen, R. L., Yancey, F. S., Chang, S. C., and Brueckner, A. L.: J. Immunol. **76**: 243, 1956.
5. Young, G. A., Kitchell, R. L., Luedke, A. J., and Sauther, J. H.: J. Am. Vet. M. A. **126**: 165, 1955.
6. Shultz, G., and De Lay, P. D.: J. Am. Vet. M. A. **127**: 225, 1955.
7. Adams, J. M., Heath, H. D., Twagawa, H. T., Jones, M. H., and Shear, H. H.: A. M. A. Am. J. Dis. Child. **92**: 109, 1956.

7a. Bellows, M. T., Hymen, M. E., and Merritt, K. K.: Pub. Health Rep. **64**: 319, 1949.

8. Arzt, L., and Kerl, W.: Wien. klin. Wchnschr. **26**: 787, 1913.
9. Dyer, I.: South. M. J. **33**: 601, 1940.
10. Shuman, H. H.: Am. J. Dis. Child. **58**: 564, 1939.
11. Siegel, M., and Greenberg, M.: J. Pediat. **49**: 280, 1946.
12. Baskin, J. L., Soule, E. H., and Mills, S. D.: Am. J. Dis. Child. **80**: 10, 1950.
13. Gregg, N. McA.: Trans. Ophth. Soc. Australia (Brit. M. A.) **4**: 119, 1944.
14. Swan, C., Tostevin, A. L., and Black, G. H. B.: M. J. Australia **2**: 889, 1946.
15. Julianelle, L. A., and Lange, A. C.: Am. J. Ophth. **21**: 890, 1938.
16. Zuelzer, W. W., and Stulberg, C. S.: A. M. A. Am. J. Dis. Child. **83**: 421, 1952.
17. Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I., Gear, J., Measroch, V., and Kirsch, Z.: J. Pediat. **48**: 1, 1956.
18. Adams, J. M.: Journal-Lancet **115**: 192, 1945.
19. Goodpasture, E. W., et al.: Am. J. Dis. Child. **57**: 997, 1939.
20. Muller, J.: Virchows Arch. Path. Anat. **238**: 481, 1922.
21. Smith, A. J., and Weidman, F. D.: Univ. Pennsylvania M. Bull. **23**: 285, 1910-1911.
22. Goodpasture, E. W., and Talbot, F. B.: Am. J. Dis. Child. **21**: 415, 1921.
23. Jackson, L.: J. Infect. Dis. **30**: 636, 1922.
24. Cole, R., and Kuttner, A. G.: J. Exper. Med. **44**: 855, 1926.
25. Kuttner, A. G., and Wang, S. H.: J. Exper. Med. **60**: 773, 1934.
26. Smith, M. G.: Am. J. Path. **32**: 641, 1956.
27. Markham, F. S.: Am. J. Path. **14**: 311, 1938.
28. Farber, S., and Wolbach, S. B.: Am. J. Path. **8**: 123, 1932.
29. McCordock, H. A., and Smith, M. G.: J. Exper. Med. **63**: 303, 1936.
30. Smith, M. G.: Am. J. Path. **32**: 641, 1956.
31. Fetterman, G. H.: Am. J. Clin. Path. **22**: 424, 1952.
32. Mercer, R. D., Luse, S., and Guyton, D. H.: Pediatrics **11**: 502, 1953.
33. Margaleth, A. M.: Pediatrics **15**: 270, 1955.
34. Birdsong, M., Smith, D. E., Mitchell, F. N., and Corey, J. H.: J. A. M. A. **162**: 1305, 1956.
35. McCordock, H. A., and Smith, M. G.: Am. J. Dis. Child. **47**: 771, 1934.
36. Smith, M. G., and Vellios, F.: Arch. Path. **50**: 862, 1950.
37. Wyatt, J. P., Saxton, J., Lee, R. S., and Pinkerton, H.: J. Pediat. **36**: 271, 1950.
38. Bacala, J. C., and Burke, R. J.: J. Pediat. **43**: 712, 1953.
39. Worth, W. A., and Howard, H. L.: Am. J. Path. **26**: 17, 1950.
40. Kinney, T. D.: Am. J. Path. **18**: 799, 1942.
41. Kidder, L. A.: Am. J. Clin. Path. **22**: 870, 1952.
42. Gallagher, H. S.: Am. J. Clin. Path. **22**: 1147, 1952.
43. France, N. E.: Arch. Dis. Child. **26**: 588, 1951.
44. Farber, S., and Craig, J. M.: J. Pediat. **48**: 800, 1956.
45. Haymaker, W., Girdany, B. R., Stephens, J., Lillie, R. D., and Fetterman, G. H.: J. Neuropath. & Exper. Neurol. **13**: 562, 1954.
46. Alexander, W. S.: J. Path. & Bact. **65**: 375, 1953.
47. Burmester, F.: Arch. path. Anat. **317**: 165, 1949.
48. Linzenmeier, G.: Ztschr. Kinderh. **71**: 162, 1952.
49. Minder, W. H.: Schweiz. med. Wchnschr. **51**: 83, 1953.
50. Diezel, P. B.: Arch. path. Anat. **325**: 109, 1954.
51. Seifert, G.: Arch. path. Anat. **325**: 586, 1954.
52. Kalfayan, B.: Arch. Path. **44**: 467, 1947.
53. Coppell, D. F., and McFarlane, M. N.: J. Path. & Bact. **59**: 385, 1947.
54. Ahvenainen, E. K.: Acta path. et microbiol. scandinav. **93**: 159, 1952.
55. Prawirohardjo, S.: Nederl. tydschr. v. geneesk. **82**: 6218, 1938.
56. Nezelof, and Rossier, A.: Etudes neo-natal. **3**: 145, 1954.
57. Potenza, L., and Klanke, H.: Arch. venezol. puericult. y pediat. **17**: 11, 22, 1954. 11, 22, 1954.
58. Weller, T. H., Macaulay, J. C., Craig, J. M., and Wirth, P.: Proc. Soc. Exper. Biol. & Med. **94**: 4, 1957.

OBSERVATIONS ON THE FAILURE OF INSULIN TO PASS FROM THE FETUS TO THE MOTHER IN THE RABBIT*

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THE problem of the passage of insulin across the mammalian placenta has considerable theoretical and practical interest. From an experimental point of view it is greatly complicated by the virtually complete dependence of the fetal blood sugar on that of the mother. On this account, the interpretation of experimental results following the injection of insulin into the mother or the fetus has been varied and conflicting and has yielded no unequivocal argument in favor of the permeability of the placenta to the hormone. We were encouraged to renew the study of this problem by the incidental discovery that the rabbit fetus is remarkably tolerant of the hypoglycemic effect of large doses of insulin. A new technique was also developed for introducing the insulin directly into the fetal blood stream through the yolk sac or vitelline circulation. Large amounts of insulin were injected in this way and the maternal blood sugar levels were followed for several hours thereafter. No evidence for the passage of insulin from the fetus to the mother was obtained.

Material and Methods

Pregnant rabbits of nondescript breed were used within a few days of term, that is on or about the twenty-seventh day. All were starved for at least 24 hours before the experiments. They were anesthetized with intravenous Nembutal sodium and the abdomen immediately opened. Samples of maternal blood were obtained from an ear vein before the injection of insulin into the fetuses, to ensure that the anesthesia and operative procedure were without significant effects on the blood sugar level. The uterus was then delivered into the abdominal wound with gentle traction. Insulin (Iletin,† 80 units) was then injected undiluted into an exposed vitelline vein in the following manner. A small incision was made over a large vitelline vessel which could be seen through the translucent wall of the uterus and a purse-string suture was placed lightly around the hole with fine silk thread. Insulin was then injected into the exposed vein in a dose of 1 ml. (80 units per fetus with a hypodermic syringe fitted with a fine (30 gauge) needle. The vitelline venous system was observed to blanch during the injection and to refill with blood immediately after the injection was completed. The small hole in the vessel was sealed after withdrawal of the needle by touching it momentarily with a crystal of silver nitrate. The fetal membranes, which are apt to prolapse, were then gently returned and the purse-string suture was drawn tight. Three fetuses were injected in this manner, the total amount

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†Eli Lilly and Company.

injected being 240 units. Maternal blood samples were taken for several hours after the injection of insulin. Fetal blood samples were obtained from injected and uninjected fetuses at the end of the experiment.

The blood sugar was estimated as total reducing substance by the method of Somogyi[1] and with a Klett-Summerson photoelectric colorimeter.

Results

The experimental results are presented in Table I. They have been divided into two groups. The results obtained in the first group of 5 animals were considered to be valid since the fetuses were found to be alive at the end of the experiment. The animals in Group 2 were technically unsatisfactory and fetal death with or without placental separation were found to have occurred.

TABLE I. BLOOD SUGAR LEVELS OF THE PREGNANT RABBIT AT TERM FOLLOWING THE INTRAFETAL INJECTION OF 240 UNITS OF INSULIN

	BLOOD SUGAR LEVELS (MG.%)											
	BEFORE INJECTION (MINUTES)		AFTER INJECTION (MINUTES)									
ANIMAL	30	5	30	45	60	75	90	105	120	135	150	175
*Group 1.**—												
1	78	114	—	76	—	66	—	76	—	—	—	—
2	81	99	—	96	—	93	—	97	—	102	—	—
3	63	72	67	—	—	56	—	46	—	48	—	—
4	87	87	58	—	—	—	76	—	—	114	—	—
5	64	75	61	90	92	—	86	—	114	—	—	—
Group 2.†—												
1	108	108	—	196	—	—	245	—	306	—	—	250
2	94	95	85	—	100	—	190	—	200	—	—	320
3	88	91	75	—	108	—	183	200	—	235	—	305
4	78	84	—	—	78	—	—	128	—	—	—	128
5	94	87	—	—	81	—	108	—	183	200	—	230

*Group 1: Technically satisfactory; placentas and fetuses intact.
†Group 2: Technically unsatisfactory; placentas damaged with or without fetal death.

Fetal blood sugar levels were obtained in 2 animals in Group 1 and gave evidence for the direct and prolonged effect of the injected insulin. In one animal (Rabbit 1) the blood sugar levels of 2 injected fetuses were 15 and 20 mg. per cent, respectively: those of 2 uninjected fetuses were 42 and 60 mg. per cent, respectively. In a second animal (Rabbit 3) the blood sugar level of an injected fetus was 6 mg. per cent and that of an uninjected fetus was 42 mg. per cent.

The insulin sensitivity of a normal pregnant rabbit under the conditions of these experiments was studied by injecting 2 units of insulin intravenously into a rabbit near term, starved overnight and subjected to the same operative procedure without the injection of insulin into the fetuses. The blood sugar of the mother fell from a preinjection level of 81 mg. per cent to a level of 27 mg. per cent at the end of an hour. No convulsions occurred.

Experiments were also carried out to determine the effect of large doses of insulin on newborn rabbits. In one experiment 2 newborn rabbits, starved overnight, were injected intraperitoneally with 80 units of insulin. Three control animals received an equal volume of isotonic saline intraperitoneally. At the end of 2 hours the blood sugar level of the injected group (pooled blood) was 10 mg. per cent: that of the control group was 117 mg. per cent

(pooled blood). In another experiment 2-day-old rabbits were injected intraperitoneally with 500, 1,000, and 1,500 units of insulin intraperitoneally. The animals were still alive 24 hours later and the blood sugar levels were too low to be recorded. No attempt was made to maintain the body temperature, a factor which may have contributed to their survival. Members of other litters of rabbits, when these became available, have been injected with small amounts of insulin and have been shown to respond by a fall in blood sugar to intraperitoneal doses as low as ½ unit.

Comment

The injection of large doses of insulin (240 units) directly into the fetal blood stream near the end of gestation has been shown to be followed by a slight fall in the maternal blood sugar levels over a 2 hour period in 2 animals and no significant change in 3 animals. The lowest recorded blood sugar levels in the 2 former animals were 44 and 66 mg. per cent, respectively, and were in each case higher than the level produced in a control rabbit injected with 2 units of insulin intravenously (27 mg. per cent in one hour). The following experimental conditions have been considered to favor the demonstration of any significant passage of insulin to the mother after the injection of the hormone into the fetuses: the fact that the rabbits were starved for at least 24 hours, thus increasing their sensitivity to insulin; the direct introduction of the insulin into the fetal blood stream via the vitelline circulation, thus eliminating any factor of delayed absorption; the use of very large doses of insulin which would have disastrous consequencees for the rabbit under ordinary conditions. In spite of these conditions no alteration took place in the maternal blood sugar level or only a slight fall of doubtful significance.

In the remaining animals in the experimental series (Group 2) an actual rise in the maternal blood sugar levels took place following the intrafetal injection of insulin. In most cases this rise was prolonged and progressive throughout the period of the experiment. In all such animals the death of one or more fetuses was found to have occurred. The phenomenon of maternal hyperglycemia following the death of a fetus is being studied further in this laboratory and is readily reproducible. It has been shown to depend on a particular kind of damage to the placenta involving the separation of its maternal and fetal elements and is not produced by simple removal of the fetuses without damage to the placentas. This phenomenon may possibly be encountered in the human female. Thus Hellmuth[2] observed that the blood sugar levels of pregnant women in the last third of pregnancy were lower than normal and that at the time of delivery their blood sugar rose to the upper limits of normal and in about 50 per cent of cases reached definitely hyperglycemic levels (up to 228 mg. per cent). Holzbach[3] observed a sudden and protracted hyperglycemia (120 to 210 mg. per cent) immediately following the observed cessation of the fetal heartbeat in a diabetic woman at the ninth month followed by the delivery some days later of a macerated fetus.

Rabbit fetuses injected with very large doses of insulin proved to be very tolerant of its hypoglycemic effect and in no instances was fetal death traceable to the effect of the insulin in the absence of placental damage. Moreover,

blood sugar levels considerably lower than those of uninjected fetuses in the same litter were observed after several hours in fetuses injected with insulin. Thus there was ample evidence that the fetuses were sensitive to insulin and that the degree of hypoglycemia induced by overwhelming doses of insulin was sufficient to counteract the steady flow of glucose across the placenta from the mother. These findings also indicated that the insulin was not inactivated during the period of the experiment.

The placental transfer of insulin from the fetus to the mother has been studied by several authors[4-10] and has been critically reviewed by Schlossmann.[11] The latter author concluded that no good evidence had been obtained for the permeability of the mammalian placenta to insulin. The results of the experiments recorded in this paper support this conclusion as far as the rabbit is concerned.

Summary

Observations are recorded on the effects on the maternal blood sugar level of injecting large doses (240 units) of insulin into the blood stream of fetal rabbits close to term. Of 5 animals successfully studied, no alteration took place in the maternal blood sugar level over a 2 hour period in three animals and a slight fall occurred in 2 animals. The lowest recorded blood sugar levels in the latter 2 animals were 66 mg. per cent and 46 mg. per cent, respectively, and were higher than that produced in a control animal following the intravenous injection of 2 units of insulin (27 mg. per cent within one hour). In 8 other animals a definite hyperglycemia was shown to follow the intrafetal injection of insulin, a phenomenon which was observed to be associated with damage to the placenta. It was concluded that no evidence was obtained to support the view that insulin can pass across the placenta from the fetus to the mother in the rabbit.

References

1. Somogyi, M.: J. Biol. Chem. **195:** 19, 1952.
2. Hellmuth, K.: Arch. Gynäk. **128:** 11, 1926.
3. Holzbach, E.: Ztschr. Gynäk. **50:** 2610, 1926.
4. Britton, S. W.: Am. J. Physiol. **95:** 178, 1930.
5. Corey, E. L.: Physiol. Zoöl. **5:** 36, 1932.
6. Macchiarulo, O.: Ann. di ostet. **52:** 559, 1930.
7. Olow, J.: Biochem. Ztschr. **217:** 475, 1930.
8. Pack, G. T., and Barber, D.: Am. J. Physiol. **92:** 466, 1929.
9. Rupp, H.: Arch. Gynäk. **143:** 741, 1930.
10. Snyder, F. F., and Hoskins, F. M.: Anat. Rec. **35:** 23, 1927.
11. Schlossmann, H.: Ergebn. physiol. **34:** 741, 1932.

THE EFFECT OF PITOCIN ON THE PLACENTA*

A Preliminary Report

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THE mechanism of action of progesterone on the myometrium (as far as we know it today) readily explains the beneficial effect of this hormone in the maintenance of pregnancy.[1, 2, 3] Progesterone drastically depresses excitability of the uterine muscle by blocking propagated activity of the cell membrane. Thus progesterone-dominated myometrium cannot be effectively excited by its intrinsic stimulatory system, nor by oxytocic drugs, nor by any type of electrical stimulation for which intact propagation is required. The progesterone-dominated uterus, although its maximum working capacity is unchanged (as can be demonstrated by applying a uniform electric field of high intensity), cannot be activated to an appreciable extent by physiological means, and a stimulus reaching the myometrium elicits only a "local response." It appears, therefore, that, as long as the progesterone block is effective, the myometrium cannot be activated as a whole, and no useful work can be performed. Csapo[2, 3] emphasized that we know of no substance which can activate the uterus when it is effectively blocked by progesterone.

If these conclusions are correct it is appropriate to ask the following question. How is it possible that, during normal pregnancy, when no activation should occur owing to the progesterone block, labor can often be induced by Pitocin several weeks before term?

Csapo offered the following explanation. In the human, at least in the second and third trimesters of pregnancy, when the placenta is presumably the chief source of progesterone, the effect of this hormone upon the uterus may be exerted locally, the hormone produced in the placenta being distributed to the uterus by diffusion. According to this view, there will be a gradient of distribution and action of progesterone in the myometrium, highest at the placental site and declining toward the opposite side of the uterus.

He also pointed out that, although the response of uterine muscle to Pitocin, as observed experimentally, is immediate, the action of this drug in inducing labor before term is delayed by several days. This indicates that the myometrium must undergo a profound change before Pitocin can finally act upon it. The only way so far known of making the myometrium sensitive to

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Pitocin is by withdrawing the progesterone block. It may therefore be assumed that, in inducing labor before term, Pitocin acts primarily by interfering with the production of progesterone in the placenta and can exert its oxytocic effect upon the myometrium only after the progesterone block has been removed. This explanation of the action of Pitocin implies that it may interfere with placental function, perhaps even causing physical damage to the placenta. This hypothesis suggested an experimental investigation of the effect of repeated Pitocin treatment on the placenta in pregnant rabbits.

Thus far only a series of preliminary experiments has been completed, which may be described as follows. Ten New Zealand white rabbits, weighing 3 to 4 kilograms, were given Pitocin in a total dose of 2 to 8 I.U. per animal on the twenty-first and twenty-second days of pregnancy. In 7 of the 10 this treatment produced hemorrhagic lesions in the placentas. At laparotomy, or autopsy, this was first recognized by a discoloration of the uterus due to hemolyzed blood within the membranes. Sections through the placentas showed hemorrhages of different sizes, from microscopically small to very large ones (Fig. 1). All the bleeding had taken place *within* the placenta, not between the placenta and the myometrial wall. This finding again suggests that the primary effect of Pitocin at this stage of pregnancy is exerted on the placenta itself and is not due to its well-known effect on the myometrium.

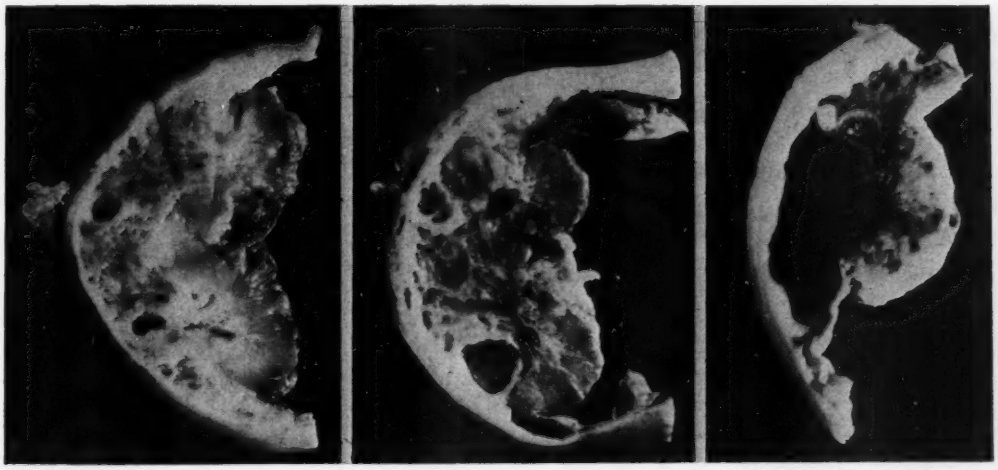

Fig. 1.—Small, medium, and large bleeding in the placenta (from left to right, respectively). Rabbit, 21 days pregnant, injected intramuscularly at 10 A.M. and 12 noon with 1 I.U. Pitocin. Autopsy at 2 P.M. Note that the bleeding occurs *within* the placenta and not between the uterine wall and the placenta.

Because of the probability that the observed damage had its primary seat in the blood vessels, the two known ingredients of Pitocin were next tried separately. In a small series (5 animals) it was shown that purified oxytocin* was insufficient even in high doses (16 I.U. per animal); on the other hand, 2 to 8 I.U. of vasopressin had a pronounced effect in all cases.

Search of the literature disclosed that effects of Pitocin similar to those described here were observed by Knaus[4] in rabbits between the seventeenth and the twenty-ninth days of pregnancy. He found that such injections resulted in fetal death and premature delivery some days later. This effect he

*Kindly supplied by Professor du Vigneaud.

attributed to bleeding in the spongy layer of the placenta which he supposed to be due to "the abnormal tearing of the uterine muscle at the joint layer of the placenta." If this were the case, however, the question would arise why these uterine contractions do not result in labor, or why in later stages of gestation the contractions during labor do not produce placental bleeding.

Parkes[5] found essentially the same effect of Pitocin in the mouse. He also concluded that the harmful effect of Pitocin on the placenta might be due to contamination by vasopressin, and he remarked that "since abortion occurs one to three days later (than the administration of Pitocin) the effect is probably due to some vascular disturbance in the placenta sufficient to cause fetal death and subsequent evacuation of the uterus." These assumptions are confirmed by our experiments as stated above.

It is evident that Pitocin (through its vasopressin contamination) produces placental bleeding only *before* term and not *at* term. This must be due to the fact that before term, when the myometrium is progesterone-blocked and therefore unable to react to oxytocin, the dose of Pitocin can be increased indefinitely without myometrial response. The vasopressin content, which is simultaneously increased, becomes large enough to produce placental hemorrhages. At term, on the other hand, the uterus is very sensitive to oxytocin, and delivery can therefore be started and completed by very small doses of Pitocin. The vasopressin content of these small quantities of Pitocin is insufficient to produce placental damage.

I feel that publication of such preliminary experiments is justified because of the clues they give for interpreting the mechanism of Pitocin-induced labor. Successful termination of pregnancy by means of Pitocin may erroneously be interpreted to mean that this is the only substance needed for activation of the myometrium. The fact, however, that, in the human patient, induction of labor several weeks before term requires Pitocin treatment for several days strongly suggests that the primary action of Pitocin in such cases does not involve the myometrium. We intend to investigate the question of whether the action of Pitocin in late pregnancy in women is similar to that in the rabbit, i.e., primarily an effect of vasopressin on the placenta.

Thus, successful termination of pregnancy by prolonged Pitocin treatment cannot be used as evidence against the significance of progesterone block in the maintenance of normal pregnancy.

My thanks are due to Dr. George W. Corner and Dr. Arpad Csapo for stimulating discussions and helpful comments on the manuscript.

References

1. Csapo, A.: The Mechanism of Myometrial Function and Its Disorders, in Bowes, Kenneth, editor: Modern Trends in Obstetrics and Gynaecology, second series, London, 1955, Butterworth & Company, Ltd., pp. 20-49.
2. Csapo, A.: Am. J. Anat. **98**: 273, 1956.
3. Csapo, A.: J. Physiol. **133**: 145, 1956.
4. Knaus, H. H.: J. Physiol. **61**: 383, 1926.
5. Parkes, A. S.: J. Physiol. **69**: 463, 1930.

OPHTHALMODYNAMOMETRY IN TOXEMIAS OF PREGNANCY

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IT HAS long been known that in the later stages of pregnancy theer may be a sudden visual catastrophe often associated with a generalized body tissue damage. It has also come to be believed that the only remedy lies in prevention. With this realization much energy has been directed toward early diagnosis, even toward the recognition of a pretoxemic state.

Recent work done by Bailliart[3] has raised the question of whether increased brachial pressure is usually the earliest manifestation of toxemia. Some cases of toxemia are seen with a normal brachial arterial pressure. It has been suggested that perhaps an increase in the arterial pressure of the small arterioles in the central nervous system is an earlier change. The arteriolar pressure in the central nervous system is well reflected in the arteriolar pressure of the retina. It was with the possibility of detecting very early signs of toxemia that these studies of retinal arterial pressures were undertaken.

Earlier Work

Work on ophthalmodynamometry comes mainly from Bailliart.[2] He was also the first to describe the relationship between retinal and brachial arterial pressures, the normal ratio being 0.45:1 for the diastolic and 0.54:1 for the systolic pressure. He pointed out that in hypertensive conditions the retinal diastolic pressures rise in proportion to the rise in brachial diastolic pressures. The rise in retinal systolic pressure, however, is proportionately greater than the rise in brachial systolic pressure, the proportion being 0.7 to 0.8:1. Bailliart was supported by Volhard,[13] who further pointed out that in essential hypertension a rise in the retinal pressure may be the earliest sign and that this is perhaps also true of the toxemias of pregnancy. Volhard's findings do not relate to the diastolic retinal pressures, for he believes that only the systolic pressure ratio between retinal and brachial pressures was altered. Bailliart, on the other hand, regarded a disproportionate rise in retinal diastolic pressure as an indication of high cerebrospinal vascular pressure.

The values of retinal systolic and diastolic pressures as reported by different observers have varied over a wide range. Magitot and Bailliart[7] found that in man the diastolic/systolic ratio varied from 25/50 to 30/70 mm. mercury. The assessment of ophthalmodynamometric data has been undertaken

by Gonzaby[5] and by Streiff,[12] who consider that the measurement of retinal pressures by this method is fairly accurate and the values obtained quite reliable for clinical purposes. Weigeli and associates[15] have pointed out the value of recording retinal arterial pressures to assess the state of intracranial circulation and consider this procedure to be of clinical significance.

The diagnostic and prognostic significance of retinal diastolic pressures in general states of hypertension has been recently stressed by many authors[1, 8, 10, 11, 16] Kologolu[6] also assessed its importance in the prognosis of eclampsia. The present study was concluded somewhat earlier than the appearance of Kologolu's report.

Technique of Recording Pressure

Local anesthesia is applied to the eye and the intraocular tension recorded. The systemic blood pressure is measured in the usual way.

The observer then sits in front of the patient as for direct ophthalmoscopy. He holds the ophthalmodynamometer in one hand and the self-illuminating ophthalmoscope in the other. The dynamometer is held like a pen with the first three fingers while the other two rest on the temporal region. The instrument is placed upon the sclera about 7.5 mm. away from the corneoscleral junction to the temporal side. Rapid but gradual pressure is applied by the instrument directed perpendicularly to the eyeball. During compression the fundus is observed with the ophthalmoscope and the large vessels at the disc are watched.

At the appearance of the first tremor or fleeting pulsation in the artery the pressure is stopped without removal of the instrument. The pointer on the disc in the dial type of ophthalmodynamometer stops and the reading is recorded. The compression is then reapplied till the pulsations stop completely, the artery collapses, the disc becomes white, and vision is lost. The reading is noted and the pressure discontinued. The figures obtained can be converted into millimeters of mercury on the table provided with the instrument.

The instrument is based on the same principle as the syphygmomanometer but instead of detecting the changes in the pulse, either by palpation or auscultation, the appearance and disappearance of the pulse in the large vascular trunks is directly observed at the disc. Duke-Elder[4] criticized this method as he feels that it records only pressures in the ophthalmic artery itself. Streiff[12] recently expressed the opinion that the method is clinically reliable and that an error of more than 1.5 mm. does not occur. We feel that the ophthalmodynamometer is comparatively accurate and is of practical clinical value.

Clinical Material

Thirty clinically normal women in various stages of pregnancy were examined for any abnormalities in the retinal and brachial pressures and for possible changes in the eye ground. Sixty women with evidence of preeclamptic or eclamptic toxemia were next examined. Retinal changes in these were also noted and arterial pressure in the brachial artery and retina recorded. Finally, 10 patients seen in the first trimester of pregnancy in whom the brachial arterial pressure and the retinal systolic pressure were within normal range but the retinal diastolic pressure was elevated have also been included in this study.

All of these have been followed during pregnancy. The findings in all these cases have been correlated with eye ground changes according to gradations of Wagner[14] and Mylius.[9] The results are summarized in Tables I and II.

TABLE I. SYSTOLIC RETINAL AND BRACHIAL ARTERIAL PRESSURES

	NO. OF CASES	EYE GROUND GRADE	RETINAL AVERAGE	RETINAL MIN.	RETINAL MAX.	BRACHIAL AVERAGE	BRACHIAL MIN.	BRACHIAL MAX.	AVERAGE RATIO
During Pregnancy.—									
Normal pregnancy									
First trimester	10	0	58	52	65	114	102	125	0.51:1
Second trimester	10	0	58	52	68	109	90	120	0.53:1
Third trimester	10	0	61	52	70	115	102	125	0.52:1
Pre-eclampsia	10	0	77	60	95	125	110	140	0.61:1
	20	1	86	65	105	138	128	158	0.62:1
	10	2	100	86	110	155	140	180	0.64:1
Eclampsia	2	0	95	95	95	140	140	140	0.68:1
	6	1	84	80	88	154	150	158	0.53:1
	8	2	104	88	112	163	155	180	0.64:1
	4	3	104	95	112	167	160	175	0.59:1
Potential toxemia	10	0	60	54	70	115	102	128	0.54:1
After Delivery.—									
Normal pregnancy	30	0	62	52	70	114	102	125	0.54:1
Pre-eclampsia	30	0	60	52	65	115	105	128	0.54:1
	10	1	72	60	90	124	100	155	0.58:1
Eclampsia	8	0	85	70	95	130	110	165	0.60:1
In the Third Trimester.—									
Potential toxemia	3	0	70	62	85	128	107	142	0.55:1
	7*	1	84	65	100	140	120	150	0.60:1

*Developed signs of toxemia.

TABLE II. DIASTOLIC RETINAL AND BRACHIAL ARTERIAL PRESSURES

	NO. OF CASES	EYE GROUND GRADES	RETINAL AVERAGE	RETINAL MIN.	RETINAL MAX.	BRACHIAL AVERAGE	BRACHIAL MIN.	BRACHIAL MAX.	AVERAGE RATIO
During Pregnancy.—									
Normal pregnancy									
First trimester	10	0	33	30	38	70	60	88	0.47:1
Second trimester	10	0	35	30	40	70	60	90	0.50:1
Third trimester	10	0	35	31	45	71	60	95	0.50:1
Pre-eclampsia	10	0	55	45	65	76	60	90	0.70:1
	20	1	62	45	75	87	70	100	0.71:1
	10	2	69	55	80	96	70	130	0.76:1
Eclampsia	2	0	60	60	60	95	95	95	0.63:1
	6	1	62	60	65	93	90	95	0.66:1
	8	2	80	72	85	99	95	100	0.81:1
	4	3	82	75	90	108	105	110	0.76:1
Potential toxemia*	10	0	45	36	54	74	60	88	0.62:1
After Delivery.—									
Normal pregnancy	30	0	35	30	45	70	60	95	0.50:1
Pre-eclampsia	30	0	55	45	60	74	65	95	0.75:1
	10	1	57	45	72	78	70	100	0.77:1
Eclampsia	8	0	68	60	80	90	80	105	0.76:1
	12	1	74	65	85	95	85	110	0.80:1
In the Third Trimester.—									
Potential toxemia	3	0	56	40	60	75	60	85	0.70:1
	7†	1	60	44	70	87	70	98	0.71:1

*Cases showing high diastolic retinal pressure.
†Developed signs of toxemia.

Comment

In normal pregnancy there is no alteration in the retinal and the brachial arterial pressures in the first trimester though later on there is a slight drop in both. The reason for this fall is not fully understood.

In the cases of pre-eclampsia in our series, the eye ground changes varied from Grade 0 to Grade 2, and in eclampsia from Grade 1 to Grade 3. The ratio between retinal and brachial systolic pressures was found to be in the neighborhood of 0.63:1 in pre-eclampsia, and 0.65:1 in eclampsia. These figures are definitely higher than those seen in normal individuals in the same month of pregnancy (0.53:1). Although there is a rise in both the brachial and retinal arterial pressures, there is evidently a disproportionate rise in the retinal systolic pressure.

The disparity is more marked if we consider the diastolic pressures. The ratio between the retinal arterial diastolic and the brachial diastolic is in the neighborhood of 0.7:1 in the normal as compared with 0.5:1 in Grades 0 and 1 of retinopathy and 0.76:1 in Grades 2 and 3 in eclampsia.

In toxemia of pregnancy a comparatively greater rise of diastolic retinal pressure should always be looked upon with special concern, as it is in these cases that eclampsia may develop. During the follow-up of toxemia cases it has also been observed that the brachial pressure begins to fall much earlier than the retinal pressure. Similarly, in a few cases of normal pregnancy regarded by us as potentially toxemic, we have noted that there is an increase particularly in retinal diastolic pressure, and that a few of these cases have subsequently passed to toxemia, and even presented Grade 1 retinal changes.

An increase in diastolic retinal pressure, even in normal pregnancy, calls for a careful and regular prenatal survey, and perhaps termination of pregnancy to prevent permanent vascular damage with detriment to maternal health. In the absence of eye ground changes, however, the pregnancy may be continued if kept under constant supervision.

Eye ground changes alone do serve as a rough guide, but need not be looked upon with such grave concern as is common today, particularly if they are associated with only a moderate rise in retinal pressure. On the other hand, if there is present a disproportionate rise in retinal arterial pressure the continuation of pregnancy is highly dangerous.

The presence of a disproportionately high retinal diastolic pressure in the absence of retinal changes calls for a careful observation, but not for a hasty termination of pregnancy. The systolic pressure in the retinal artery shows an erratic trend and therefore we do not attach much importance to this change.

It has been suggested that the retinal organic changes parallel a rise in brachial pressure, but this is not always true. On the other hand, we have observed that retinal organic change does parallel the retinal diastolic pressure. We therefore regard retinal diastolic pressure as a better indication of probable organic vascular changes.

Retinal arteries are comparable to the arterioles of the central nervous system. Changes in these suggest a comparable change in the central nervous system. Similarly, pressure changes in the retinal arteries probably reflect the changes in the pressure in the arterioles of the central nervous system. This concept is suggested by Miller and Audoueineix[8] in relation to general hypertension.

Perhaps the retinal arteries may also be compared with the arterioles of the kidney. Renal damage might then be anticipated, proportionate to the rise in retinal diastolic pressure. Hypertension of pregnancy is, of course, not to be regarded as a manifestation of primary kidney damage, but on the contrary it should be considered a sign of generalized vascular disorder.

Summary

1. Thirty cases of normal pregnancy have been studied for brachial and retinal pressures. It has been found that in the later months both are somewhat reduced.

2. In 10 cases of normal pregnancy which we regarded as potentially toxemic, a high retinal diastolic pressure was observed. A number of these patients became toxemic, suggesting that the retinal arterioles are the first to be affected, and indicating the importance of retinal diastolic pressures.

3. There is a disproportionate rise in the retinal diastolic pressure in pre-eclampsia and in eclampsia. The greater the disproportion, the graver is the prognosis.

4. The retinal changes in the form of retinopathy can be correlated more accurately with the retinal diastolic pressure than with brachial pressure.

5. Changes in the central nervous system and in the kidney arterioles probably occur simultaneously and perhaps can be gauged by the retinal damage.

6. Ophthalmodynomometry is recommended as a routine technique for investigation in pregnancy.

References

1. Azcoga, J. M.: Arch. Soc. oftal. hispano-am. **5**: 519, 1945.
2. Bailliart, P.: Clin. opht. **15**: 178, 1928.
3. Bailliart, P.: Vascular Affections of the Retina, Paris, 1953, Gaston Doin & Cie.
4. Duke-Elder, S. W.: Text Book of Ophthalmology, London, 1940, Henry Kimpton, vol. 1.
5. Gonzaby, N. B.: Arch. Soc. oftal. hispano-am. **15**: 262, 1955.
6. Kologolu, S.: Yeni Klin. J. **1**: 98, 1955.
7. Magitot, A., and Bailliart, P.: Am. J. Ophth. **5**: 824, 1922.
8. Miller, H. A., and Audoueineix, E.: Trans. Ophth. Soc. U. Kingdom **75**: 391, 1955.
9. Mylius, K.: Abhandl. a. d. Augenh. u. ihr. Grenzgeb. **1**: 6, 1927.
10. Nigro, Lactitia: Riv. oto-neuro-oftal. **24**: 409, 1949.
11. Pavia, J. L.: Am. J. Ophth. **41**: 85, 1956.
12. Streiff, E. B., and Bischler, V.: Ophthalmologica **112**: 19, 1946.
13. Volhard, I.: Verhandl. deutsch. Gesellsch. inn. Med. **33**: 422, 1921.
14. Wagner, H. P.: J. A. M. A. **101**: 1381, 1933.
15. Weigeli, H., Althanes, H., Burhard, C., Reckmann, P., and Assendroff, J.: Docum. ophth. **7-8**: 183, 1954.
16. Wilbrandt, R.: Helvet. med. acta **18**: 553, 1951.

"NITROGENOUS RETENTION" IN PATIENTS WITH TOXEMIA OF PREGNANCY—AN UNUSUAL COMPLICATION OF SALT RESTRICTION*

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SALT restriction is one of the most uniformly accepted adjuncts to the therapeutic armamentarium used in the hypertensive toxemias of pregnancy. The limitation of salt has proved to be of definite therapeutic value and has often been acclaimed to be an important prophylactic measure against the development of toxemia. The recent observations of Dieckmann and associates[1] suggest that pure pregnancy toxemia may be differentiated from other varieties of nonspecific hypertensive disease by the sodium-retaining capacity of the patient. These observations emphasize the important role that sodium metabolism plays in the deranged physiology inseparably linked with the toxemias of pregnancy. In addition to the abnormal sodium metabolism of this patients, defects in nitrogenous waste excretion are frequently observed. In 1934 Stander and Cadden[2] studied nonprotein nitrogen and uric acid blood levels in normal and in pre-eclamptic and eclamptic patients. They observed that the blood nonprotein nitrogen concentration rose late in the course of pre-eclampsia and eclampsia. A much greater increase in the blood concentration of uric acid was observed in these patients, with an abrupt rise immediately following a convulsive seizure. They concluded that the accumulation of uric acid in the blood of the eclamptic patient resulted from basic metabolic changes presumably in the liver and not from decreased renal function. They were careful to state that their data did not eliminate the possibility that uric acid excretion was decreased in eclampsia, and concluded that there was a definite parallelism between the severity of the pre-eclampsia or eclampsia and the blood concentrations of uric acid. In a subsequent publication these authors[3] reported data obtained from 5 eclamptic patients which supported their previous contention that uric acid excretion was not decreased in this disease. In accordance with these observations, early termination of pregnancy by induction of labor or even by cesarean section has been frequently advocated.

Chesley[4] in 1950 reinvestigated the question of urea and uric acid clearances in toxemia. He reported that in pre-eclampsia there was a 30 per cent reduction in urea clearance and a 54 per cent reduction in uric acid clearance

*Aided in part by the Edward G. Schlieder Educational Foundation of New Orleans, La.

when compared to normal pregnancy. He could not demonstrate a consistent relationship between the severity of the disease and the degree of reduction of uric acid clearance. He also observed that occasionally a pre-eclamptic patient responded to the usual therapeutic methods and was "cured" according to accepted clinical criteria, even though she remained unimproved or actually became worse as judged by a constant reduction or even an actual progressive decline in uric acid clearance.

The observations of Chesley[4] and similar observations of our own have stimulated the study of hypertensive toxemic patients, who, during hospitalization, are characterized by clinical improvement associated with increasing blood concentrations of uric acid and urea. For simplicity, increased blood concentrations of uric acid and urea will henceforth in this paper be designated "nitrogenous retention."

During the past three years a large number of patients have been admitted to the Louisiana State University inpatient unit of the obstetric service at Charity Hospital of Louisiana at New Orleans with the preliminary diagnosis of severe hypertensive toxemia of pregnancy. These patients were maintained on strict bed rest with the exception of daily weighing. Blood pressure determinations were obtained and recorded every two to four hours. They routinely received a 2,500 calorie diet containing 100 grams of protein and 30 meq. of sodium. No limitation was placed on the quantity of water consumed. Mild basal sedation was produced by the oral administration of 120 mg. of sodium phenobarbital four times daily. No specific vasodilator agents were employed on the patients included in this investigation. Routine laboratory studies consisting of urinalyses for protein, blood urea, and plasma uric acid determinations, serum proteins, and hematocrits were performed upon admission and approximately twice weekly thereafter. The blood urea nitrogen was determined by the method of Karr[5] as modified by Kingsley.[6] The plasma uric acid was determined on protein-free plasma filtrate utilizing the (Folin-Denis) phosphotungstic acid-carbonate colorimetric method. The Coleman Junior spectrophotometer was used. Occasionally, other laboratory studies were conducted. These included the phenolsulfonphthalein (P.S.P.) test, urea clearances, and serum and urine electrolyte determinations. A small number of patients managed in this manner developed laboratory signs of progressive nitrogenous retention during their prenatal hospitalization.

This present preliminary report consists of the presentation of data obtained from a series of 7 such patients. In addition, definitive therapeutic measures and basic etiological implications suggested by these data are discussed.

Presentation of Data

The clinical and laboratory data obtained from these seven patients are presented in Table I. The average age of these patients was 30 years. Their average parity was 7.7, and their average weight at the time of admission was 171 pounds. The average blood pressure upon admission was 185/113 mm. Hg. Six of the 7 patients were classified as having hypertensive cardiovascular disease with superimposed pre-eclampsia. The seventh patient presumably

TABLE I. INTERVAL CLINICAL AND LABORATORY DATA

PATIENT	AGE	PARITY	HOSPITAL DAY	WEIGHT (POUNDS)	BLOOD PRESSURE (MM. Hg)	EDEMA	URINALYSIS (PROTEIN)	BLOOD UREA NITROGEN (MG. %)	PLASMA URIC ACID (MG. %)	SERUM ELECTROLYTES (MEQ./L.) Na	K	Cl	P.S.P. (15 MIN.)	CUMULATIVE SODIUM INTAKE (MEQ.)	DIAGNOSIS
M. S.	37	vi	1	166	190/120	0	2+	12.0	2.6	–	–	–		30.0	Hypertensive cardiovascular disease + pre-eclampsia
			2										30%		
			6	158	140/ 90	0	0	26.4	3.4	131.3	5.38	100.7		180.0	
			14 Del.	157	130/ 96	0	0	28.0	4.4	133.0	4.82	102.1		420.0	
T. B.	29	viii	1	150	170/110	0	1+	14.8	4.1	–	–	–		30.0	Hypertensive cardiovascular disease + pre-eclampsia
			6	144	126/ 86	0	0	20.2	6.3	129.4	5.71	95.7		103.2*	
			18 Del.	142	110/ 80	0	0	37.0	8.4	126.0	6.20	93.7		151.6*	
R. J.	24	iv	1	Not recorded	230/130	0	1+	11.2	2.4	–	–	–		30.0	Hypertensive cardiovascular disease + pre-eclampsia
			2	Not recorded	180/110	0	1+	–	–	131.6	3.64	100.3		60.0	
			19 Del.	135	130/110	0	0	25.6	6.2	132.7	6.56	100.8		570.0	
L. P.	33	xiv	1	152	160/100	1+	Trace	9.2	3.6	–	–	–		30.0	Hypertensive cardiovascular disease + pre-eclampsia
			6	146	140/ 90	0	0	11.4	4.7	–	–	–		180.0	
			28 Del.	145	110/ 70	0	0	26.6	5.9	127.7	5.29	100.8		840.0	
R. T.	14	0	1	201	145/ 95	Trace	0	13.4	4.0	–	–	–		30.0	Pre-eclampsia
			10	196	130/ 90	0	0	19.2	4.4	132.9	4.5	105.8		300.0	
			15										35%		
			32 Del.	187	120/ 80	0	0	25.8	6.7	131.1	5.14	102.6		960.0	
V. J.	36	x	1	118	200/110	2+	Trace	14.8	3.6	–	–	–		30.0	Hypertensive cardiovascular disease + pre-eclampsia
			4										5%		
			8	106	156/ 90	0	0	40.0	5.0	130.4	5.88	97.3		240.0	
			16										25%		
			48 Del.	For complete data see Table II and Fig. 2											
L. C.	40	xii	1	242	200/130	4+	1+	7.6	4.0	–	–	–		30.0	Hypertensive cardiovascular disease + pre-eclampsia
			20	221	130/100	0	0	25.2	5.5	131.1	–	103.8		600.0	
			23	220	140/100	0	0	25.6	7.2	130.9	5.94	104.7		690.0	
			29 Del.	For complete data see Table III											

*4.4 meq. Na daily (special diet).

had only pre-eclampsia. The average duration of the prenatal hospitalization was 26.7 days with a range of from 14 to 48 days. On the day of admission 4 of the 7 patients had a trace to four plus edema and 6 of the 7 had proteinuria. The initial concentrations of urea and uric acid in the blood were within the normal range, the mean of the seven being 11.9 and 3.4 mg. per cent, respectively. During the prenatal hospitalization, the clinical course of these patients was characterized by a significant decrease of both systolic and diastolic blood pressure, by significant loss of weight, and by the disappearance of both edema and proteinuria. These changes represented a partial reversal of certain clinical features of the disease and hence implied a general clinical improvement. Several of these patients, however, developed various degrees of mental apathy, generalized skeletal muscle weakness, and diminished skin turgor. This clinical picture suggested that a hyponatremic

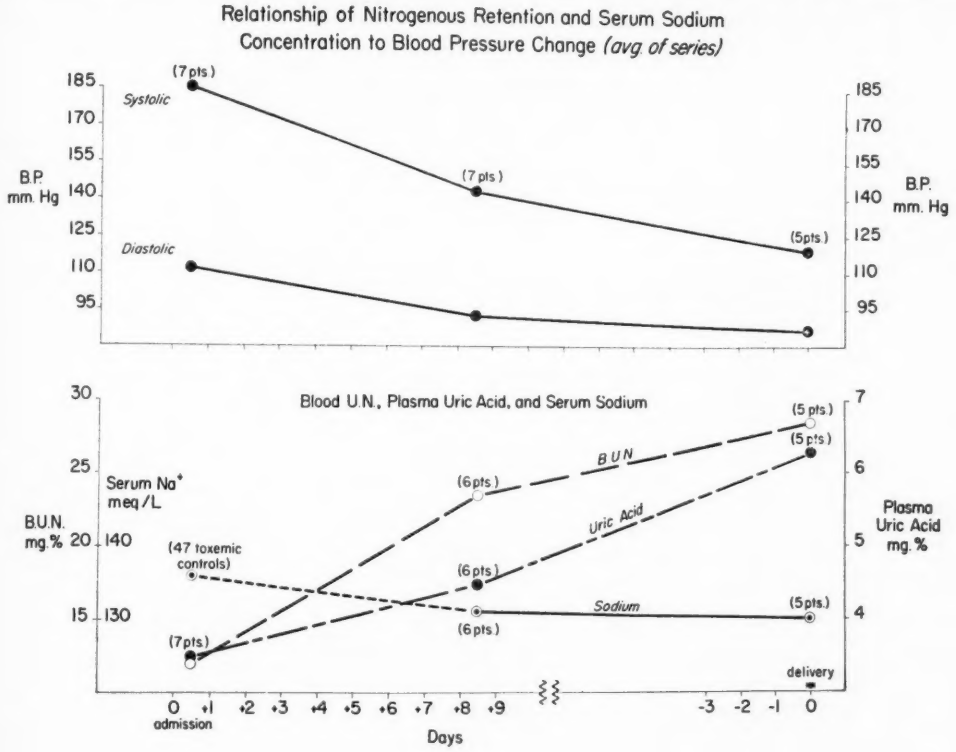

Fig. 1.

state had developed. In order to investigate this possibility, serum electrolyte determinations were added to the laboratory program. Serial serum sodium, potassium, and chloride determinations were performed on 6 of the 7 patients in this series. The initial serum electrolyte concentrations are listed in Table I. Five of the 7 initial determinations were done within the first 10 days after admission. The mean value for the sodium concentrations obtained from these 5 initial determinations was 131.1 meq. per liter. The corresponding mean values for potassium and for chloride were 5.02 and 100.0 meq. per liter, respectively. Corresponding blood urea and plasma uric acid determinations were also obtained. The means of these were 23.4 and 4.8 mg. per cent, respectively. These changes in blood urea and plasma uric acid represent a 96.6 per cent increase in urea concentration and a 41.2 per cent increase in the

TABLE II. INTERVAL CLINICAL AND LABORATORY DATA ON PATIENT V. J.

	HOSPITAL DAY														
	1	4 AND 5	7	8	9	13	24	25	26	27	28	33	44	46	48
Blood pressure	170/108	–	140/90	155/90	156/100	160/100	150/100	140/90	140/102	160/100	150/100	152/100	150/100	150/110	–
Weight (pounds)	118	–	107	106	–	–	–	–	–	–	–	–	103	103	–
Blood urea nitrogen (mg. %)	14.8	–	38.8	40.0	27.4	17.8	30.8	21.8	–	18.0	18.0	14.8	29.2	22.4	Del.
Plasma uric acid (mg. %)	3.6	–	5.0	5.0	–	4.1	5.5	–	–	4.7	4.7	3.3	3.5	4.0	–
Serum electrolytes (meq./L.)															
Na				130.4	133.7	137.0	128.6	130.4	132.2	133.3	132.4	134.1	132.8	133.2	–
K				5.88	5.42	4.61	4.86	4.40	3.90	4.19	4.04	5.06	5.11	4.83	–
Cl				97.3	102.7	103.8	102.7	105.4	107.5	108.0	105.9	101.6	101.6	103.2	–
Na intake (meq.)															
Oral*															
Intravenous				304.0	214.0	–	366.0	366.0	366.0	214.0	428.0	–	428.0	–	–
Urine Na (meq.)				171.0	–	–	–	–	206.0	167.0	227.0	–	–	248.0	–
Urine volume (c.c./day)			3,550	4,097	–	–	–	–	5,750	4,250	4,568	3,100	–	–	–
Kidney function	P.S.P. 30% Urea clearance 30%					(Hosp. day 16) P.S.P. 60%								(Hosp. day 47) Urea clearance 81%	

*Daily oral intake of Na = 30 meq.

uric acid concentration. An additional correlation between blood urea and plasma uric acid and serum electrolyte concentrations was made on the day of delivery for 5* of these patients. The average blood urea concentration on this day was 28.6 mg. per cent and that of plasma uric acid was 6.3 mg. per cent. At the same time, the mean serum sodium, potassium, and chloride concentrations were 130.1, 5.6, and 100.0 meq. per liter, respectively.

A comparison of the blood urea and plasma uric acid concentrations found on the day of admission with those obtained on the day of delivery disclosed that the urea concentration had increased 140.3 per cent and that the uric acid concentration had increased 85.3 per cent. The blood pressure changes during the prenatal hospitalization and the blood urea, plasma uric acid, and serum sodium concentrations are summarized in Fig. 1. It can be seen that there is an inverse relationship betwen the blood pressure

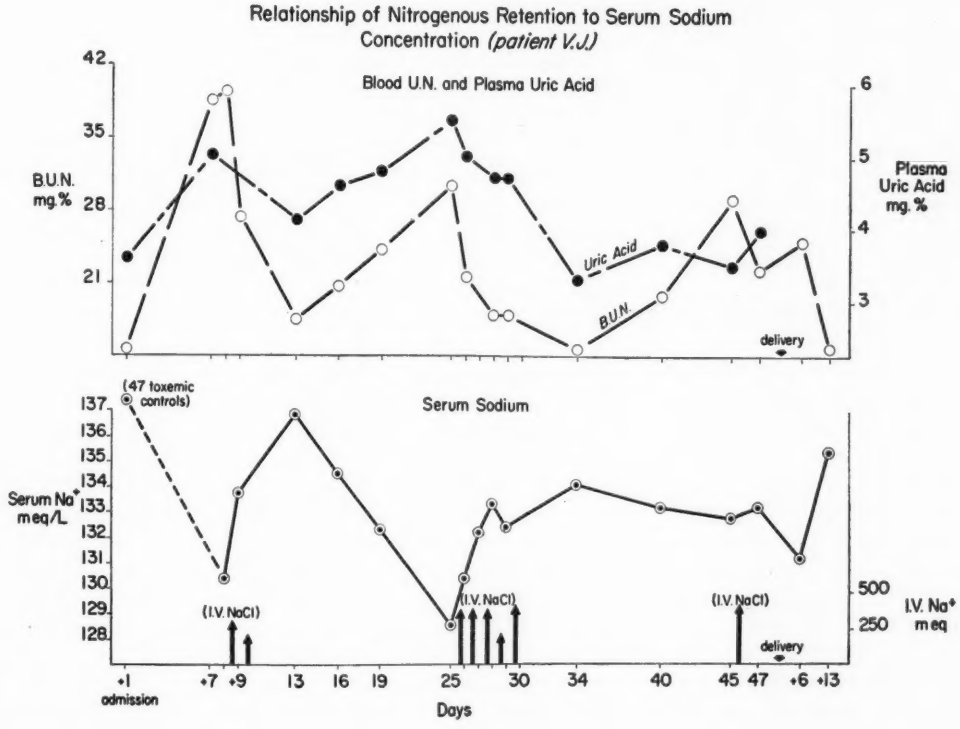

Fig. 2.

and the concentrations of urea and uric acid in the blood. It should be noted that the first serum electrolyte determinations were done on these 7 patients approximately 8 days after admission. The electrolyte analyses obtained on these patients are included in Table I and in Fig. 1. In order to establish a theoretical value for the serum concentration of sodium on the day of admission, the average of the serum sodium concentrations obtained by this laboratory on 47 "clinically comparable" toxemic patients on the day of admission was obtained. This figure was found to be 137.5 meq. per liter. This theoretical value is incorporated in Fig. 1. As illustrated in Fig. 1, the sodium

*The data obtained from patients V. J. and L. C. are intentionally excluded from the laboratory correlation made on the day of delivery but will be presented in detail later in this report.

TABLE III. INTERVAL CLINICAL AND LABORATORY DATA ON PATIENT L. C.

	HOSPITAL DAY												
	1	2	6	9	13	18	20	23	24	25	27	28	29
Blood pressure (mm. Hg)	180/120	170/110	160/110	140/100	140/100	140/100	130/100	140/100	140/100	140/100	140/100	120/90	Del.
Weight (pounds)	242	232	228	225	225	222	222	–	–	–	217	216	–
Blood Urea Nitrogen (mg. %)	7.6	5.2	7.8	5.0	12.0	21.8	25.2	25.6	–	–	13.0	–	–
Plasma uric acid (mg. %)	4.0	3.5	4.5	4.2	5.0	7.3	5.5	7.2	–	–	6.6	–	–
Serum electrolytes (meq./L.)													
Na	–	–	–	–	–	–	131.1	–	130.9	131.7	–	130.0	–
K	–	–	–	–	–	–	–	–	5.94	–	–	6.21	–
Cl	–	–	–	–	–	–	103.8	–	104.7	103.7	–	105.3	–
Na intake (meq.)													
Oral*													
Intravenous	–	–	–	–	–	–	–	–	304.0	–	–	–	–

*Daily oral intake of Na = 30 meq.

TABLE IV. INTERVAL CLINICAL AND LABORATORY DATA ON PATIENT T. B.

	HOSPITAL DAY													
	1	4	7	8	9	10	11	12	13	14	15	16	DE-LIVERY 18	19
Blood pressure	170/110	120/80	126/86	110/70	120/80	100/68	110/80	110/80	118/80	120/80	120/80	120/80	110/80	110/70
Weight (pounds)	150	144	144	142	143	143	142	142	143	142	142	–	142	–
Blood urea nitrogen (mg. %)	13.8	–	20.2	–	18.8	20.8	28.2	24.7	–	–	21.4	–	37.0	–
Plasma uric acid (mg. %)	4.1	–	6.3	–	7.3	6.7	5.7	6.7	–	–	4.0		8.4	–
Serum electrolytes (meq./L.)														
Na	–	129.4	–	128.2	128.5	125.9	124.9	124.5	–	123.4	123.6	121.4	126.0	127.6
K	–	5.71	–	5.07	5.62	6.93	5.25	5.07	–	5.88	5.07	5.34	6.20	5.94
Cl	–	95.7	–	97.4	98.9	96.8	95.2	95.2	–	93.1	88.9	91.5	93.7	91.5
Na intake (meq.)														
Oral	30	4.35	4.35	4.35	4.35	4.35	4.35	4.35	4.35	4.35	4.35	4.35	4.35	30.0
Urine Na (meq.)	–	37	43	39	27	18	13	15	11	10	10	17	25	50
Urine volume (c.c./day)	–	2,410	2,780	2,470	1,850	1,625	1,190	1,350	1,110	1,200	1,450	770	1,510	2,175

concentrations may have gradually and progressively decreased during the period of prenatal hospitalization. The average sodium concentration of these patients at the time of delivery is considerably lower than that obtained at a comparable time by this laboratory on a large number of nontoxemic patients who had not been on any controlled prenatal salt limitation regime.

The concurrent appearance of progressive nitrogenous retention and hyponatremia together with marked reduction in blood pressure and significant weight loss suggested that this clinical entity might represent a variety of the "low salt syndrome." In order to examine this hypothesis, it was decided to administer a solution of sodium chloride intravenously to a prenatal toxemic patient who showed all of the clinical and laboratory manifestations of the "low salt syndrome." This therapeutic trial was performed on two patients, V. J., and L. C. The clinical data on both of these patients are listed in Table I. In general, these two patients presented similar clinical characteristics upon admission. Both were elderly multiparas and had severe hypertension. Both showed edema and minimal proteinuria. Their blood urea and plasma uric acid concentrations were within normal limits. Both patients had clinical diagnoses of hypertensive cardiovascular disease with superimposed pre-eclampsia. The complete clinical and laboratory data on one of these patients are tabulated in Table II and illustrated graphically in Fig. 2. From the latter it can be seen that the blood concentrations of urea increased during the first 7 days after admission from 14.8 to 38.8 mg. per cent, representing a 162 per cent increase. There was a corresponding increase in plasma uric acid concentrations from 3.6 to 5.0 mg. per cent, representing a 39 per cent increase. On the fourth day of hospitalization, presumably during the development of azotemia, the P.S.P. excretion rate was found to be 30 per cent in two hours. On the following day, the urea clearance was 30.4 per cent of normal. The blood urea determination was repeated on the eighth day and found to be 40.0 mg. per cent. At this time serum electrolyte determinations showed the sodium to be 130.4, the potassium 5.88, and the chloride to be 97.3 meq. per liter. On the basis of these findings, the patient was given intravenously 304 meq. of sodium in "physiologic" saline solution. The administration of this salt solution was completed in approximately 6 hours. No untoward reactions occurred. Approximately 14 hours later blood urea and serum electrolyte determinations were repeated. The urea concentration had decreased to 27.4 mg. per cent, representing a 32 per cent decrease. The sodium concentration in the serum increased from 130.4 to 133.7 meq. per liter. Because the sodium concentration remained relatively low, an additional 214 meq. of sodium was administered intravenously in the form of 5 per cent sodium chloride in water. Four days later the blood urea concentration was 17.8 mg. per cent and the plasma uric acid concentration was 4.1 mg. per cent. These represent total percentage decreases in the urea and uric acid concentrations of 56 and 18 per cent, respectively. It is significant that the urea and uric acid concentrations in the blood persisted at relatively high levels on days 7 and 8 even though the urinary volume was more than sufficient to effect "maximal" clearance rates for both of these substances. Apparently, the administration of sodium chloride to the patient resulted in a significant lowering of the blood levels of urea and uric acid. The serum sodium concentration at this time had increased to 137.0 meq. per liter. Three days later, the two hour P.S.P. excretion rate was 60 per cent.

During the next 11 days, serial blood urea, plasma uric acid, and serum electrolyte analyses were performed. The reciprocal relationship between the urea and uric acid concentrations and the serum sodium levels was again found. On the twenty-fourth day the blood urea concentration had increased

to 30.8 mg. per cent, whereas the serum concentration of sodium had decreased to 128.6 meq. per liter. Additional sodium chloride given intravenously again effected a reversal of the upward trend of urea and uric acid concentrations. This entire cycle was repeated a third time with similar but somewhat less dramatic results. The urea clearance determined one day prior to delivery and 3 days after the last administration of sodium chloride was 81 per cent of normal. No major changes in the blood pressure resulted from the administration of the sodium chloride. The highest pressures recorded for this patient were on the day of admission.

It is apparent from Table III that in patient L. C. there were no significant changes in blood urea and plasma uric acid concentrations during the first 9 days of hospitalization. Shortly thereafter a rapid increase in concentration of both substances occcurred. On the twenty-third day after admission the blood urea and plasma uric acid concentrations were 25.6 and 7.2 mg. per cent, respectively. On the following day the serum sodium, potassium, and chloride concentrations were 130.9, 5.94, and 104.7 meq. per liter, respectively. Three hundred and four meq. of sodium was then given intravenously. A small and perhaps insignificant increase in the sodium concentration occurred the following day. Three days after the sodium chloride had been given, the concentrations of urea and uric acid had decreased to 13.0 and 6.6 mg. per cent, but the sodium concentration had not changed significantly. Before additional sodium chloride could be given, however, labor and delivery occurred. Laboratory and clinical facilities did not permit complete sodium balance studies on any of these patients. Limited data were, however, obtained relative to the urinary sodium output in 2 patients, V. J., and T. B. It is apparent from Table II that patient V. J. excreted fairly large quantities of sodium. There was also a high sodium intake from the sodium chloride therapy. The sodium output in the urine on the days studied was consistently less than the total sodium intake. More extensive sodium intake and urinary output data were obtained on patient T. B. and are shown in Table IV. This patient was on a very limited sodium intake (4.35 meq. per day). Her urinary sodium output was quite small but consistently exceeded the sodium intake. She received no sodium chloride therapeutically.

TABLE V. LABOR AND DELIVERY DATA*

PATIENT	DURATION OF PREGNANCY (WEEKS)	LABOR	WEIGHT OF BABY
M. S.	32	Spontaneous	6 pounds, 8 ounces
T. B.	39	Spontaneous	6 pounds, 6 ounces
R. J.	36	Induced (because of azotemia)	4 pounds, 4 ounces
L. P.	40	Cesarean section (repeat)	4 pounds, 2 ounces
R. T.	39	Spontaneous	4 pounds, 15 ounces
V. J.	38	Spontaneous	4 pounds, 5 ounces
L. C.	40	Spontaneous	7 pounds, 2 ounces

*All babies were born alive and in good condition except the stillborn infant of M. S.

Data pertaining to the labor and delivery of the 7 patients are presented in Table V. It is perhaps significant that 3 of the patients, L. P., R. T., and V. J., who were delivered at or near term, had babies that weighed less than 5 pounds. Patient M. S. was delivered at term of a 6 pound, 8 ounce stillborn fetus. Pregnancy was terminated for patient R. J. because of progressing

nitrogenous retention. It should be noted that this procedure antedated the observations which demonstrated that the administration of sodium chloride in certain instances effected a reversal of azotemia.

Comment

The clinical and laboratory observations described in this report suggest that in these patients a rapid reduction in kidney function occurred coincident with hospitalization and salt limitation. The kidney function was altered in such a way that blood concentrations of urea and uric acid were significantly increased. The azotemia was in each instance associated with hyponatremia. This relationship between salt depletion and increased nonprotein nitrogen concentration in the blood was first suggested by Hartmann and Smyth[7] in 1926. Their observations were made on pediatric patients. In this present report the apparent relationship between hyponatremia and impaired kidney function was clearly demonstrated by effecting a reversal of the azotemia in two patients by means of the intravenous administration of sodium chloride solutions. No significant increases in blood pressure were produced by the administration of sodium chloride.

The rapid development of a clinical entity which appears to be identified with the "low salt syndrome" described by Schroeder[8] suggests that excessive sodium loss may have occurred. The laboratory data relative to urinary excretion of sodium by the patients included in this report are very limited but do suggest that the sodium losses exceeded those which one would expect in normal patients under similar sodium intake regimes. There appear to be two plausible explanations for this sodium loss. One possibility is that an organic lesion in the renal tubules makes them refractory or nonresponsive to the sodium-retaining corticoids elaborated by the adrenal cortex or perhaps by the placenta. This clinical entity has been designated "salt losing nephritis" by Thorn and associates.[9] Another possibility is the presence of adrenal cortical or placental inadequacy which indirectly may reduce the rate of renal tubular reabsorption of sodium. Both of these possibilities must be examined critically with particular reference to the clinical entity described in this report.

The salt losing nephritis syndrome described by Thorn and co-workers[9] is accompanied by irreversible damage to the kidney tubules. These pathological changes are usually associated with severe degrees of hyponatremia, azotemia, and dehydration. Kidney function tests such as urea clearances and phenolsulfonphthalein excretion rates indicate extensive impairment. Murphy and associates[10] estimated that the P.S.P. excretion rate for this entity was consistently less than 10 per cent in two hours. Mental confusion, lassitude, and muscular weakness were frequently observed in these patients. In addition, salt losing nephritis is characteristically associated with marked hypotension.

A brief review of the clinical and laboratory data obtained on the day of admission on the patients described in this report permits the conclusion that in all probability no severe pre-existing renal disease was present. Renal function was determined in 3 of these patients at one time or another during their hospitalization. The 15 minute P.S.P. excretion rate for M. S. was 30 per cent and for R. T. was 35 per cent on the second and tenth days, respectively. These are considered to be normal. The third patient, V. J., had a 15 minute excretion rate of 5 per cent on the fourth day and 25 per cent when the P.S.P. was repeated on the sixteenth day. This evidence of improved renal function may be related to the administration of sodium chloride. A

fourth patient, T. B., was admitted near term for her ninth pregnancy, approximately one year later. At this time the 15 minute P.S.P. excretion rate was 30 per cent. This was repeated four months after delivery and was found to be 45 per cent. In addition to these data, the patients reported upon here had no azotemia initially; they were not dehydrated, and on admission there was no evidence of mental confusion, lassitude, muscular weakness, or hypotension. Subsequently these signs and symptoms of hyponatremia appeared in several of these patients.

Adrenal cortical deficiency could effect excessive sodium loss and other manifestations of renal functional impairment, such as azotemia, decreased P.S.P. tests, etc. In patients with known adrenocortical deficiency, renal functional impairment can be effectively and completely reversed by means of either sodium administration or adrenal cortical substitution therapy. It becomes apparent that the clinical entity described in this report could readily be accounted for on the basis of diminished adrenal cortical function. The relationship of placental steroid neogenesis to this entity remains unknown at the present time. The data obtained from these patients lend support to the observations of Marshall and Davis[11] which indicated that there seemed to be a direct relationship between the functional capacity of the adrenal gland and the ability of the kidney to excrete satisfactorily urea, creatinine, and phenolsulfonphthalein. In addition these authors stated that this relationship was apparently not dependent upon specific blood pressure levels.

Although there was a moderate decrease in blood pressure during the prenatal hospitalization of the patients presented in this series, there was no significant diminution in daily urine volume. It seems unlikely then that the azotemia which developed could be attributed to reduce renal function secondary to relative systemic hypotension.

These data suggest that the therapeutic use of sodium chloride in toxemic patients who are manifesting nitrogenous retention during a sodium restriction regime *may obviate the apparent necessity for premature termination of pregnancy.* This is, of course, predicated upon the assumption that termination of pregnancy is indicated solely by the development of nitrogenous retension.

The coexistence of adrenal cortical inadequacy and the hypertensive toxemias of pregnancy has been suggested by Tatum and Mulé.[12] It is perhaps significant that more than 50 per cent of the patients who manifested the puerperal vasomotor collapse syndrome described by these investigators were patients who had hypertensive cardiovascular disease and superimposed pre-eclampsia. Many investigators have observed the frequent coexistence of small infarcted placentas and prematurity of the baby, when prematurity is judged by weight of the baby rather than by the gestational age. This relationship has been observed frequently in patients with essential hypertension and superimposed pre-eclampsia. Whether or not there is a correlation between the adrenal cortical inadequacy suggested in this investigation and maldevelopment or malfunction of the placenta remains an enigma.

Studies in progress at the present time are directed toward definitive evaluation of adrenal cortical function and placental function by means of urinary corticoid and steroid analyses. In addition, the effects of adrenal corticoid substitution therapy on patients with this syndrome will be determined.

Summary and Conclusions

1. Seven patients with hypertensive toxemias of pregnancy developed "nitrogenous retention" during hospitalization for treatment of their toxemia. A routine limited sodium diet was employed.

2. Each of these patients manifested an improvement in clinical condition as measured by a decrease in blood pressure and by a decrease or disappearance of proteinuria and edema.

3. During hospitalization a decrease in concentration of sodium in the serum occurred simultaneously with increases in blood concentrations of urea and uric acid.

4. A therapeutic trial of the intravenous administration of solutions of sodium chloride was employed in 2 of these patients. The "nitrogenous retention" in these 2 patients was effectively reversed by this procedure.

5. It is apparent that a variety of the "low salt syndrome" was produced in these patients as a result of routine sodium chloride limitation.

6. The data suggested that excessive sodium losses in these patients could be more plausibly explained on the basis of diminished adrenal cortical function or altered placental steroid metabolism rather than on primary renal insufficiency.

7. The observations reported here suggest that the development of "nitrogenous retention" in pregnant patients with hypertensive toxemias may not necessarily require termination of pregnancy based upon maternal indication, especially when these patients coincidentally manifest definite clinical evidence of improvement. Whether or not the development of this syndrome provides a fetal indication for terminating pregnancy remains unanswered at the present time.

8. Dietary restriction of sodium chloride for patients with toxemia of pregnancy is extremely important and should be continually emphasized, even though it may result in occasional complications.

References

1. Dieckmann, W. J., Pottinger, R. E., and Rynkiewicz, L. M.: Am. J. Obst. & Gynec. **63**: 783, 1952.
2. Stander, H. J., and Cadden, J. F.: Am. J. Obst. & Gynec. **28**: 856, 1934.
3. Cadden, J. F., and Stander, H. J.: Am. J. Obst. & Gynec. **37**: 37, 1939.
4. Chesley, L. C.: Am. J. Obst. & Gynec. **59**: 960, 1950.
5. Karr, W. G.: J. Lab. & Clin. Med. **9**: 328, 1924.
6. Kingsley, G. R.: J. Lab. & Clin. Med. **29**: 337, 1944.
7. Hartmann, A. F., and Smyth, F. S.: Am. J. Dis. Child. **32**: 1, 1926.
8. Schroeder, H. A.: J. A. M. A. **141**: 117, 1949.
9 Thorn, G. W., Koepf, G. F., and Clinton, M., Jr.: New England J. Med. **231**: 76, 1944.
10. Murphy, R. V., Coffman, E. W., Pringle, B. H., and Iseri, L. T.: A. M. A. Arch. Int. Med. **90**: 750, 1952.
11. Marshall, E. K, Jr., and Davis, D. M.: J. Pharmacol. & Exper. Therap. **8**: 525, 1916.
12. Tatum, H. J., and Mulé, J. G.: Am. J. Obst. & Gynec. **71**: 492, 1956.

ABO BLOOD GROUPS IN OBSTETRICS

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CONSIDERABLE attention in the past decade has been focused on the Rh factor and its relationship to fetal mortality. While some of the more recently discovered blood group antigens, as well as the ABO system, are also known to cause hemolytic disease of the newborn, the Rh factor has received main consideration. It is the general impression that the ABO blood groups, except as transfusion problems, are of little physiologic significance in obstetrics. Evidence is accumulating that this is indeed not the case.

There is a well known and considerable variation in the percentage of blood group A, B, O, and AB individuals in different races and geographic areas. This of course is also true of the Rh factor and other blood groups and subgroups. Geneticists presume that the initial existence of these ABO antigens is the result of one or more genetic mutations and that the subsequent changes in population incidence must either be a result of isolation and inbreeding of peoples or of natural selection.[13] The former was long thought to be true, and such instances as the almost complete absence of the B gene among South American Indians and Australian aborigines is explained by the supposition that when the populations were small these genes were lost purely by chance through breeding.

The Rh system, however, is definitely affected by natural selection (as in erythroblastosis fetalis) which tends to eliminate the heterozygotes and thus reduce the existing polymorphism. The ABO blood system is also being shown to be affected by forms of natural selection.[14] Whereas large geographic areas show a relatively stable background of genes of other systems, the ABO gene frequencies vary widely over small distances, and this suggests a more intense selection by environment.[13] Any natural selection that tends to eliminate individuals in the reproductive age or to cause fetal loss must of necessity be important to obstetricians.

Erythroblastosis Fetalis

As previously noted, some minimal degree of natural selection is being exercised by ABO maternal-fetal incompatibility and development of erythroblastosis. In this country, hemolytic disease of the newborn is seen in approximately 1 out of 150 to 1 out of 200 viable pregnancies. Those cases directly due to ABO incompatibility are estimated at 1 in 3,000 pregnancies.[5] While admittedly a small number, the present birth rate in the United States will

include about 1,400 infants yearly in this category. They are less likely to be initially recognized than the Rh-sensitized infant, and there must be an appreciable fetal loss.

Fertility

For some years an apparent differential fertility has been suggested where mother and father belonged to different blood groups. Waterhouse and Hogben[20] in 1947 concluded that there was a highly significant deficiency of group A children from matings of group O mothers and group A fathers. Such matings are also said to produce fewer offspring than do matings of an O father and an A mother. Kirk and associates[10, 11] analyzed about 26,000 deliveries in Australia and felt that group A women had a higher average number of pregnancies than did group O women. The deficiency of group A (and apparently group B) children born to group O mothers was not present in the first pregnancy, was present in the second, and was greatest in third-born children. These findings may suggest some type of immunization mechanism.

While there are conflicting reports, it seems definite that the ABO blood groups do result in a selective loss of incompatible children, and that there is a gradual reduction of fertility, or perhaps reproductivity, due to this selection. Further studies in the future will likely give a clearer answer as to both cause and specific effect.

Toxemia

The most recent interest in the natural selectivity of the ABO groups was stimulated by Aird, Bentall, and Roberts[1] when they reported in 1953 that patients suffering from gastric carcinoma were more often of blood group A than was the general population. A second paper[2] noted that individuals of group O were 35 per cent more liable to peptic ulcer, whereas in carcinoma of the breast, colon, rectum, and bronchus blood group frequencies were those of the general population. Gastric carcinoma, however, does not often affect individuals in the reproductive age and peptic ulcer would seem to be only a moderate factor in these age groups. Of considerably greater interest to obstetricians was the initial report of Pike and Dickens[17] of the significantly higher proportion of group O women who developed toxemia of pregnancy.

In 3,651 consecutive patients admitted to the hospital they used the presence of two of the three following criteria for the diagnosis of pre-eclampsia: (a) blood pressure of 140/90 or above after the twenty-eighth week of pregnancy, (b) clinical edema or 1 pound weight gain in a week, (c) albuminuria in a catheterized noninfected specimen. Five hundred and forty-one cases of toxemia were found, with an 18 per cent increased incidence in patients of group O and a corresponding decrease in other groups, compared with control groups of their other obstetric patients and comparable blood groups of 20,000 pregnant women in the same area. Two recent reports,[6, 16] one by the same authors,[6] have served to contradict the original findings. It is also of interest to note that in blood group distributions such as were present in their study, about 32 per cent of group O mothers could carry a heterospecific fetus, as against about 6 per cent of group A.

The relationship of possible isoimmunization to pre-eclampsia has been investigated since 1905,[8] even before there was general knowledge of the ABO blood groups. Suggestions raised along this line[12, 15] have been subsequently discarded. Dieckmann[7] stated, "It has been shown conclusively that there is no relation between the occurrence of eclampsia and a difference of blood groups in the fetus and the mother." He cited the work of Hurst[9] who found 9 incompatible blood groups in the infants of 31 mothers with toxemia (29 per cent) and 37 in a series of 166 infants of mothers without toxemia (22 per cent)—an insignificant difference. Of the 37 normal mothers with blood-group-incompatible infants, 9 had a significant rise in isoagglutinin titer one week post partum. An appreciable rise occurred in 6 of the 9 toxemic mothers.

About the same time, however, it was reported by another author[19] that there was a significant and specific rise in maternal isoagglutinin titers when the fetus possessed A or B agglutinogens lacking in the mother's blood. When no such rise occurred, the fetus was a nonsecretor. It should be noted here that the secretion, or ability to secrete, as opposed to the nonsecretion of group-specific substances in body fluids (i.e., saliva, amniotic fluid) is a property possessed by varying numbers of individuals, depending on race and geographic location. The property appears to be due to a single dominant "S" gene, but it is also apparently interrelated with the recently discovered Lewis blood group system whose genetics are incompletely understood.

Isoimmunization could likely occur with a heterospecific fetus who was a secretor without any actual passage of fetal red cells across the placental barrier, since the group-specific antigens could pass the intact placenta. However, fetal hemoglobin in the maternal circulation has been reported, highly significant concentrations occurring in one case of Rh sensitization and in one case of toxemia.[4]

In consideration of the conflicting reports, we wished to determine blood group frequencies among our pre-eclamptic patients. Control blood group frequencies were first calculated both from 1,000 consecutive blood bank groupings in our hospital and then for all presently registered obstetric patients (Table I). These were originally subdivided into Rh positive and Rh negative, but since these groups followed the general expectation in all calculations that detail is not given here.

The obstetric records were further subdivided into those patients para 0, para i, and para ii and greater, to see if there was a discernible differential fertility. While there was a slight decrease in group O mothers and a slight increase in group A mothers among patients para ii or more, the small figures are not significant.

Records of all patients with the diagnosis of toxemia of pregnancy since 1947, when routine blood grouping of prenatal patients began, were obtained. Those which corresponded to the criteria of Pike and Dickens for the diagnosis of pre-eclampsia totaled 146. Over this period of nine years there were 10,687 deliveries, so that the incidence of pre-eclampsia is low (1.4 per cent) as compared to the 15 per cent reported by Pike and Dickens. We should note, however, that their 541 patients were almost equally divided between primigravidas and multigravidas, the latter group being hospitalized only for some complication—perhaps toxemia.

Our cases were divided as indicated in Table II. If groups O and A are compared with the controls, chi square is 9.97, yielding a probability less than .01 for one degree of freedom. If all groups are compared with the controls, chi square is 10.71 and the probability is less than .02 for three degrees of freedom. Routine blood groupings of infants were not available. In our patients 35 per cent of O mothers could carry a heterospecific fetus, as opposed to 7.5 per cent of group A.

TABLE I. CONTROL BLOOD GROUP FREQUENCIES

BLOOD GROUP	BLOOD BANK PATIENTS		OBSTETRICAL PATIENTS	
	NUMBER	%	NUMBER	%
O	416	41.6	339	42.8
A	416	41.6	341	43.0
B	119	11.9	81	10.0
AB	49	4.9	33	4.2

TABLE II. BLOOD GROUP FREQUENCIES IN TOXEMIC PATIENTS

BLOOD GROUP	TOXEMIC PATIENTS		OBSTETRICAL CONTROLS
	NO.	%	(%)
O	81	55.5	42.8
A	46	31.5	43.0
B	15	10.3	10.0
AB	4	2.7	4.2

Comment

We by no means imply that all toxemia is on a basis of ABO isoimmunization. While the possibilities of bearing a heterospecific fetus have been pointed out, many cases of toxemia certainly do occur in group A and B mothers as well as group AB mothers whose fetuses cannot be heterospecific. There appears to be a somewhat greater susceptibility of group O mothers, and perhaps this increase results from some cases of toxemia due to isoimmunization. The work of Smith and Hurst and associates shows some definite rises in maternal titers in the first postpartum week, and this may account for instances of toxemia appearing post partum which are difficult to explain by most theories extant. We hope others can either confirm or deny this possible relation of the ABO blood groups to toxemia with larger numbers of cases.

Whether the apparent decreased reproductivity of group O mothers is on the basis of increased toxemia or, since it appears to occur with multiparity, is on some other basis, is purely in the realm of speculation.

Dieckmann has discussed at some length the considerable differences in the incidence of pre-eclampsia and eclampsia in various areas of the world. This has been postulated as due to either of two causes, variations in diet and variations in climate. It would be of interest to know if these differences might in part be accounted for by the varying blood group frequencies in geographic areas.

Toxemia is stated to be rare in natives of the Dutch East Indies, Siam, Hawaii, and Alaska, as well as in many areas of Africa, India, the Persian Gulf, Hungary, and Turkey. Some of these areas are definitely low in O gene frequency, Hungary and Turkey especially, while others, excluding Africa, have a somewhat low group O incidence with correspondingly high incidence

of either groups A or B. The varying races in Africa have a relatively high frequency of group O. Recent studies of the Lewis blood system and secretors, however, have shown at least West African people to have a high percentage of nonsecretors in the population.[13]

A recent report[3] pointed out a marked racial variation in the incidence of pre-eclampsia and eclampsia in the Fiji Islands, the natives having few cases compared to those among laborers imported from India in the late nineteenth century. The blood group frequencies for the natives are: O—43.5 per cent, A—34 per cent, B—16.5 per cent, and AB—6 per cent.[18] Those for the Indian laborers are unknown. It would be most interesting to know, in studying this problem of the etiology of pre-eclampsia, what the blood group frequencies are among the Indians, and the percentage of secretors and nonsecretors in the Fijian population.

Summary

1. Evidence is accumulating that the ABO genes are not "neutral," but are affected by natural selection.

2. Such natural selection would be of obstetric importance.

3. ABO incompatibilities cause a small percentage of cases of erythroblastosis fetalis.

4. Group O mothers appear to have a lowered reproductivity as compared to mothers of other blood groups. The cause is uncertain, as is the exact degree of effect.

5. Group O mothers may have a higher incidence of pre-eclampsia.

6. Maternal isoimmunization by an ABO heterospecific fetus is a possible cause of some cases of pre-eclampsia.

7. Further studies should throw more light on these interesting problems.

References

1. Aird, I., Bentall, H. H., and Roberts, J. A. F.: Brit. M. J. **1**: 799, 1953.
2. Aird, I., Bentall, H. H., Mehigan, J. A., and Roberts, J. A. F.: Brit. M. J. **2**: 315, 1954.
3. Bell, M. E., and Willis, L.: J. Obst. & Gynaec. Brit. Emp. **62**: 917, 1955.
4. Bromberg, Y. M., Salzberger, M., and Abrahamov, A.: Obst. & Gynec. **7**: 672, 1956.
5. Davidsohn, Israel: Obst. & Gynec. **8**: 318, 1956.
6. Dickens, A. M., Richardson, J. R. E., Pike, L. A., and Fraser Roberts, J. A.: Brit. M. J. **1**: 776, 1956.
7. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, 1952, The C. V. Mosby Company.
8. Dienst, A.: Zentralbl. Gynäk. **29**: 353, 1905.
9. Hurst, J. G., Taylor, H. C., Jr., and Wiener, A. S.: Blood **1**: 234, 1946.
10. Kirk, R. L., Kirk, N., and Stenhouse, N. S.: Brit. J. Prev. & Social Med. **7**: 1, 1953.
11. Kirk, R. L., Stenhouse, N. S., Shield, J. W., Bryce, L. M., and Jakobwicz, R.: Brit. J. Prev. & Social Med. **9**: 104, 1955.
12. McQuarrie, I.: Bull. Johns Hopkins Hosp. **34**: 51, 1923.
13. Mourant, A. E.: The Distribution of Human Blood Groups, Springfield, Ill., 1954, Charles C Thomas, Publisher.
14. Neel, J. V.: Am. J. Human Genet. **6**: 208, 1954.
15. Ottenberg, R.: J. A. M. A. **81**: 295, 1923.
16. Pearson, M. G., and Pinker, G. D.: Brit. M. J. **1**: 777, 1956.
17. Pike, L. A., and Dickens, A. M.: Brit. M. J. **2**: 321, 1954.
18. Simmons, R. T., Graham, J. J., and Barnes, G.: M. J. Australia **1**: 529, 1945.
19. Smith, G. H.: J. Path. & Bact. **57**: 113, 1945.
20. Waterhouse, J. A. H., and Hogben, L.: Brit. J. Social Med. **1**: 17, 1947.

THE MANAGEMENT OF SECONDARY ABDOMINAL PREGNANCY

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BECAUSE an ectopic pregnancy tends to be a self-limiting process, the surgical management is usually not a difficult problem. Salpingectomy or salpingo-oophorectomy, combined with adequate blood replacement, is sufficient treatment. One of the exceptions is the case in which there has occurred a secondary implantation of the placenta in the abdominal cavity. Great vascularity at the points of attachment of placental tissue imposes the burden of a difficult decision on the surgeon. While removal of this tissue seems desirable to ensure optimal and rapid recovery, its dissection can provoke hemorrhage that is difficult or even impossible to control.

For this reason, it has been advocated that the placenta be left undisturbed unless invasion is confined to a limited area[2, 9] or, following fetal death, sufficient thrombosis of the placental site largely eliminates the threat of hemorrhage.[6]

If every abdominal pregnancy reached the point of viability, the safest operation probably would be removal of the fetus by laparotomy, leaving the placenta undisturbed—the latter to be excised at a later date or eliminated by a process of absorption.[3, 4, 5, 8] Few cases should progress this far, however, because, in almost every instance, there are early signs and symptoms which suggest a diagnosis of ectopic pregnancy.[7] Proper evaluation will result in earlier surgical intervention and a higher percentage of complete primary operations.

This contention is borne out by a review of the cases of secondary abdominal pregnancy treated at the Los Angeles County General Hospital during the past ten years. In this period there were 23 cases demonstrating clear-cut evidence of placental attachment to peritoneal surfaces and continued intra-abdominal growth of a fetus. All but 4 patients had symptoms beginning during the first 20 weeks and all but 5 were operated upon before the twenty-eighth week. Of the 3 patients who reached term, one had symptoms at 8 weeks and one at 12 weeks. The third had two pregnancy tests, ordered because the enlargement of the uterus did not seem to be consistent with the menstrual history.

Incidence.—In this institution, the ratio of abdominal pregnancy to other forms of ectopic pregnancy was about 1 to 40, and the ratio to reportable births was about 1 to 3,000. Seventy-four per cent of the patients were Negroes, almost double the expected incidence, since the average hospital Negro population was 38 per cent. The average patient was 30 years of age,

the average parity was 1.5, and the average number of abortions was 0.67. Two infants survived, 2 patients subsequently became pregnant, and there was one maternal death.

Pathological Findings.—In all of the observed cases, the ectopic process originated in a Fallopian tube, probably in the ampullar portion. Usually the placenta extended through the mouth of the tube, to become attached secondarily to the posterior surface of the broad ligament and uterus. The adjacent ovary was partly or wholly involved. Continued growth was to the cul-de-sac and rectosigmoid, but the attachments in these areas were more apt to be formed by adhesions than by placental invasion. In advanced cases, the omentum and loops of small bowel became adherent to the ectopic process.

While part of the placenta remained in the tubal lumen, the fetus was extruded into the abdominal cavity where it was found either floating free or enveloped by membranes. All cases conformed to this general pattern except 2. In these the fetus was first extruded into the space between the leaves of the broad ligament, and then into the pelvic cavity.

In no instance was a ureter damaged or a major blood vessel invaded. In one case, the placenta perforated the wall of the rectosigmoid. In another, fetal hair was passed per rectum, but no perforation could be demonstrated at operation. Implantations on the anterior abdominal wall or in the upper abdomen were not encountered.

While abdominal pregnancy is known to be associated with a high percentage of gross fetal abnormalities, none were noted in this series.

Diagnosis.—The clinical picture of abdominal pregnancy is not easily recognized. Among 23 cases reviewed, there were 14 erroneous initial diagnoses. However, preoperative diagnosis was abdominal pregnancy in 7 cases, and ectopic pregnancy in 10 cases. Ectopic pregnancy was considered in 3 of 6 cases incorrectly diagnosed.

The most consistent symptoms are those associated with other forms of ectopic pregnancy—amenorrhea, vaginal bleeding, and lower abdominal pain. In addition, abdominal signs and symptoms are particularly common.[8, 10] Nausea and vomiting can be excessive. Abdominal distention and tenderness are often present. The ectopic mass is easily mistaken for a pregnant uterus, although the examiner may record that the fundus was difficult to outline. Frequently, the cervix will be sharply displaced, either laterally or anteriorly, a finding which should suggest the proper diagnosis. If pregnancy is advanced, the clinical picture is most often confused with abruptio placentae. An adnexal or cul-de-sac mass may be noted, or at least some fullness or tenderness in these areas.

A typical temperature elevation will be 0.5 to 1.0° F. An average hemoglobin determination is 10 Gm., and the white blood count ranges between 12 and 15 thousand.

If an extrauterine pregnancy is suspected, certain tests are available to aid diagnosis[1]:

Colpocentesis and paracentesis (abdominal tap) were used in 13 cases. Five of 6 abdominal taps demonstrated free intraperitoneal blood, confirming a diagnosis of either abdominal or ectopic pregnancy. In the sixth case, the test was negative but the correct diagnosis was deduced from the clinical picture. Six of 7 colpocenteses demonstrated blood. In the seventh case, a dry tap was due to the fact that no free blood was present. This patient carried her pregnancy to term and was delivered of a stillborn infant.

A Friedman test, if positive, helps to establish that an adnexal mass is due to an ectopic gestation. In one case, the diagnosis of abdominal pregnancy as opposed to inflammatory disease was made on the strength of a positive test. On the other hand, the correct diagnosis was twice rejected on the basis of a negative test.

In 5 of 6 cases where an x-ray was taken, the radiologist saw nothing that suggested abdominal pregnancy. In the sixth case, the fetal shadow was visualized abnormally high, complete placental separation having allowed the fetus to gravitate to the upper abdomen. In 2 cases, the uterine cavity was found to be empty, once by sounding, the other time by dilatation and curettage. In neither case did the procedure aid in the diagnosis.

Surgical Management.—Once the diagnosis is established, abdominal pregnancy is treated by laparotomy. Because of the imminent dangers of severe intra-abdominal hemorrhage or perforation of the bowel, operation is usually performed as soon as the patient can be properly prepared for surgery. There are two possible exceptions to this rule: (1) If it is known that the infant has just died, a short period of delay might allow the vessels of the placental site to thrombose; bleeding at the time of operation will then be materially reduced and the operation made easier. (2) It has been recommended that delay is justified to permit an infant of borderline viability to gain added maturity.[2, 9] However, the hazards of expectant treatment are both unpredictable and grave.

The principal aim of preoperative preparation is to provide adequate blood replacement. Not only must precedent blood loss be restored, but rapid and excessive surgical loss should be anticipated. In this series, the average blood replacement was 2,300 c.c. and the maximum was 5,000 c.c.

The management of the placenta is the major decision to be made at operation. One must decide whether removal can be accomplished with hemostasis and with optimal conservation of the involved structures. Often the problem is complicated by pre-existing hemorrhage and adhesions which obscure the operative field. Moreover, the slightest manipulations may provoke additional bleeding of alarming proportions.

In this series, removal was accomplished in all but 4 cases—one early and 3 advanced. The procedure did not prove extremely difficult. Often the placenta came free with only blunt dissection. Although initial blood loss was heavy, it was controlled by ligation of individual bleeding points, by additional surgery such as salpingectomy or hysterectomy, or by local hemostatic agents (7 cases). In one case, it was necessary to leave a gauze pack over the placental site because of excessive blood loss (3,500 c.c.). The pack was removed in six days; a resulting wound abscess required two additional hospital admissions. Significant postoperative bleeding was not observed in any case.

In 4 instances the placenta was not removed:

1. This patient had a 28 weeks' gestation with an estimated 2 pound living infant. The placenta was attached to the posterior surface of the uterus, sigmoid colon, and bowel mesentery. Removal was not attempted. Postoperative recovery was uncomplicated except for moderately severe ileus. Subsequently, the patient refused admission for secondary removal of the placenta. Fourteen months after operation she was readmitted to the hospital with an abdominal abscess which ruptured under observation, nearly proving fatal. A second abscess formed four years later. Treatment was in another hospital.

2. A patient with a term gestation was admitted from an outside hospital two days after fetal death. The placenta was attached to the uterine fundus, broad ligament, tube, cul-de-sac, and small bowel. Removal was not attempted. Postoperative recovery was

TABLE I. FINDINGS, TREATMENT, AND

CASE NO.	AGE	RACE	VIABLE PREGNANCIES	ABORTIONS	WEEK OF FIRST SYMPTOM	DAYS OF OBSERVATION WITHOUT DIAGNOSIS	WEEK OF OPERATION	FETUS (CROWN-RUMP MEASUREMENT IN CM.)	HEMOGLOBIN (GRAMS/100 C.C.)	BLOOD REPLACEMENT (C.C.)	DIAGNOSTIC PROCEDURES
1	36	White	2	0	6	0	10	6.5	8.5	1,500	Positive colopuncture
2	32	Negro	4	0	7	27	11	"3 months' size"	8	5,000	Positive abdominal tap
3	29	Negro	0	0	8	0	11	6.5	7	2,000	Positive abdominal tap
4	32	Negro	0	1	8	7	12	7	11	1,000	Negative Friedman
5	35	White	4	1	13	0	15	7	11	2,000	Positive colopuncture
6	24	Negro	0	1	11	3	14	12	7	1,500	Positive abdominal tap
7	33	Negro	1	0	10	1	14	14	12	1,500	—
8	33	Negro	0	0	14	0	14	13	9	2,000	—
9	29	Negro	4	0	8	3	16	12	11	5,000	Positive colopuncture
10	40	Negro	2	0	10	10	16	14	10	2,000	Positive Friedman, negative abdominal tap
11	30	White	4	0	8	15	17	14	10	1,500	Positive colopuncture
12	34	Negro	3	1	17	0	17	14	6.5	2,000	Positive abdominal tap
13	30	Negro	0	1	13	7	17	15	11	5,000	Positive abdominal tap
14	27	Negro	0	1	12	12	20	19 Born alive	10	2,500	Positive Friedman
15	26	White	1	1 Ectopic	8	0	20	10	8	1,500	Positive colopuncture
16	18	White	1	0	20	2	22	"20 weeks' size" Born alive	9	2,000	—
17	19	Negro	1	0	21	30	24	20	10	2,500	—
18	29	Negro	0	1	22	1½	25	22	10	2,500	Positive colopuncture
19	31	Negro	3	0	24	0	28	2 pounds (approx.) Survived	11	2,000	—
20	32	White	3	2	6	26	34	20	12	500	—
21	28	Negro	2	6	12	1	38	5 pounds, 2 ounces Survived	10	2,500	Positive colopuncture
22	18	Negro	0	0	40	56	41	6 pounds, 14 ounces Stillborn	10	2,000	—
23	30	Negro	0	0	8	37	45	5 pounds, 14 ounces Stillborn	9	2,000	Negative colopuncture

PLACENTA		ADDITIONAL SURGERY	MATERNAL RESULTS
ATTACHMENTS	DISPOSITION		
Cul-de-sac, ovary, sigmoid, tube, small bowel	Removed. Local Oxycel	Right salpingo-oophorectomy. Colpotomy (later)	Chronic pelvic pain
Tube, posterior broad ligament	Removed	Right salpingectomy	Recovered
Tube, cul-de-sac, broad ligament, sigmoid	Removed. Hot packs, Gelfoam	Subtotal hysterectomy, bilateral salpingectomy	Removal of ovarian cyst one year later
Tube, ovary, broad ligament	Removed	Right salpingo-oophorectomy	Recovered
Tube, ovary, mesosalpinx	Removed	Right salpingo-oophorectomy	Apparently recovered
Tube omentum, broad ligament, posterior uterus, large and small bowel	Removed. Local Oxycel	Right salpingo-oophorectomy	Recovered
Tube, small bowel, superior surface of uterus	Removed	Release of adhesions	Recovered
Tube, broad ligament	Removed	Left salpingectomy	Recovered
Broad ligament, right pelvic wall, large and small bowel, cul-de-sac	Removed. Local Gelfoam 5 yard pack	Subtotal hysterectomy	Admitted twice for wound abscess
Tube, sigmoid, broad ligament, posterior uterus	Removed. Local Gelfoam. Hot packs	Left salpingo-oophorectomy	Recovered
Tube, ovary, cul-de-sac, sigmoid, omentum	Removed. Local thromboplastin	Right salpingo-oophorectomy. Omental resection	Recovered
Tube, ovary, broad ligament, cul-de-sac	Removed	Right salpingo-oophorectomy	Term delivery (3 years later)
Tube, ovary, broad ligament, sigmoid	Not removed. Local Oxycel	Left salpingo-oophorectomy	Oxycel granuloma
Broad ligament, cul-de-sac, sigmoid	Removed. Local Gelfoam and thromboplastin	—	Recovered
Tube, ovary	Removed	Left salpingo-oophorectomy	Tubal pregnancy (6 months later)
Tube, ovary, broad ligament	Removed	Left salpingo-oophorectomy	Recovered
Tube, ovary, posterior, uterus, large and small bowel	Removed	Subtotal hysterectomy, left oophorectomy, bilateral salpingectomy, colostomy	Recovered. Colostomy closure
Tube ovary cul-de-sac, ileum, sigmoid	Removed (spontaneous detachment)	Loop colostomy, closure of sigmoid perforation	Death from fecal peritonitis
Posterior uterus, bowel mesentery	Not removed	—	Ruptured abdominal abscess
Tube, ovary, broad ligament	Removed	Subtotal hysterectomy, left salpingectomy, right salpingo-oophorectomy	Carcinoma of cervical stump. Five-year survival
Uterus, cul-de-sac, appendix, sigmoid, cecum, small bowel	Not removed. 5 yard abdominal pack	—	Total hysterectomy, bilateral salpingo-oophorectomy (7 months later)
Tube, uterus, broad ligament, small bowel cul-de-sac	Not removed	—	Subtotal hysterectomy, left salpingo-oophorectomy
Tube, omentum, broad ligament, small bowel mesentery	Removed	Right salpingectomy	Pseudocyesis

stormy, complicated by ileus and pneumonitis. The patient made a good recovery. Five weeks later she was readmitted because of a fever ranging to 104° F. Response to antibiotics was unsatisfactory and one week later a laparotomy was performed. The placenta was firmly attached to the uterine fundus and left tube, and loosely attached to the cul-de-sac, sigmoid colon, and small bowel. Removal was not difficult and bleeding was minimal. Subtotal hysterectomy was necessary because the left cornual area of the uterus was replaced by a large, necrotic crater. Postoperative recovery was complicated by a superficial wound abscess.

3. This was a 17 weeks' gestation with a 15 cm. living fetus. The placenta was attached to the right broad ligament, cul-de-sac, and rectosigmoid colon. Removal was attempted but abandoned because of excessive bleeding. Twelve pieces of Oxycel were packed into the bleeding area. After ten minutes' observation, during which the rate of blood loss appeared to be diminishing, the abdomen was closed without drainage. The postoperative course was complicated by infection of the mass in the cul-de-sac and 69 days of hospitalization were necessary. An Oxycel granuloma formed which was still present three years after operation.

4. The patient was 38 weeks pregnant with a 5 pound, 2 ounce living infant. The placenta was attached to the posterior surface of the uterus, cul-de-sac, pelvic wall, cecum, small bowel, and appendix. Removal was not attempted. However, during the process of extracting the fetus, profuse hemorrhage began at the placental edge. The estimated blood loss was 2,000 c.c. This was controlled by a gauze pack brought through the incision and removed on the fourth day. Two and one-half months after operation, the placental mass became infected. Ten days' hospitalization, treatment with antibiotics, and two transfusions were required. Seven months after the original operation, the placental mass was excised, along with the uterus, tubes, and both ovaries which had become extensively involved in the inflammatory process.

A measure of the amount of injury to adjacent organs is shown in Table I. Portions of abdominal organs were removed in 18 of the 23 cases, either because of extensive local damage or hemorrhage which could not otherwise be controlled. In 2 cases, the rectosigmoid was involved by invasion:

1. Evidence for invasion was the passage of fetal hair per rectum. The fetal head was impacted in the cul-de-sac. At operation no gross defect could be found in the bowel wall. Nevertheless, it was decided to sidetrack the fecal stream by a sigmoid colostomy. Postoperative recovery was uneventful and the colostomy was closed at a later date.

2. The patient was admitted to the hospital in the twenty-fifth week of pregnancy with signs and symptoms of generalized peritonitis. At operation the placenta was found to be detached from an implantation on the right adnexa, cul-de-sac, and sigmoid colon. There was a 2 cm. perforation of the rectosigmoid. After removal of the products of gestation and repair of the bowel perforation, a transverse loop colostomy was made. The patient died four days later of an overwhelming fecal peritonitis. This represents the only maternal death of this series.

Comment

In the management of secondary abdominal pregnancy, primary removal of the placental tissue is desirable because it promises a shorter convalescence, fewer postoperative complications, and no secondary operations.

Primary removal is possible, particularly if an early diagnosis is made, when the ectopic process is limited to structures that can conveniently be excised; such as tube, ovary, or broad ligament. Even in more advanced cases, it is sometimes possible to perform a complete operation because the

bulk of the intra-abdominal attachments are in the form of separable adhesions and actual placental invasion is confined to a relatively small area. Prior death of the fetus also favors placental dissection because thrombosis of the placental bed reduces operative hemorrhage. On the other hand, primary removal is not always feasible, since it can be accompanied by rapid and prodigious blood loss. Also, there is always the possibility that the placenta has invaded a structure that cannot be easily or safely repaired. Prior blood loss and extensive adhesions make adequate dissection more difficult. Finally, primary surgery may sacrifice pelvic organs which could have been salvaged by a more conservative procedure.

The treatment of 23 cases of secondary abdominal pregnancy has been discussed. Early signs and symptoms were usually present. Although diagnosis was apt to be delayed, an operation was performed in the first half of pregnancy in 15, and before viability in 18 of the 23 cases. Operation was performed in the previable period in 18 cases with the following results:

1. Fifteen cases: Complete removal of the placenta with satisfactory hemostasis and recovery of the patient. At times the surgical blood loss was heavy.

2. One case: Successful excision of the placenta but continued bleeding from the implantation site requiring gauze pack. Recovery was complicated by a wound abscess.

3. One case: Dissection of the placenta was abandoned because of rapid blood loss. Although hemorrhage was controlled by Oxycel, a troublesome residual granuloma formed in the cul-de-sac.

4. One case: The placenta spontaneously separated, disclosing a perforation of the colon. The patient died of fecal peritonitis which had been established prior to admission to the hospital.

Five cases had advanced to 28 weeks. One fetus was previable, however, having been dead some weeks:

1. Two cases: Prior fetal death had initiated thrombosis of the placental site. Complete excision of the placenta was accomplished without difficulty. Recovery was uneventful.

2. One case: While only the fetus was removed, the edge of the placenta was accidentally separated. A gauze pack controlled hemorrhage but led to widespread infection of all the pelvic organs.

3. Two cases: The retained placenta became infected. In one instance, it was removed secondarily with sacrifice of the uterus. In the other, an abdominal abscess of near-lethal proportions ensued.

It is concluded that the placental tissue of secondary abdominal pregnancy should be removed whenever possible in order to avoid further complications and additional operations. The surgeon should be qualified to deal with all phases of abdominal surgery and be prepared to replace large amounts of blood loss. The factors which favor removal are as follows:

1. Diagnosis before the point of viability—the earlier the better.

2. Placental *invasion* confined to removable organs such as tube, ovary, uterus, and broad ligament.

3. Thrombosis of the placental site.

When carried to completion, removal was accomplished with adequate hemostasis and without damage to adjacent abdominal organs. When removal was not accomplished, there were major complications and prolonged convalescence.

Summary

A group of 23 cases of secondary abdominal pregnancy are presented. In the majority of cases, complete primary removal of the placenta was accomplished. The factors favoring removal are discussed and some of the hazards noted. Adequate blood replacement is essential. If primary removal of the placenta is not possible, subsequent complications are likely. An early diagnosis favors complete operation because removal is less difficult during the first half of pregnancy.

References

1. Beacham, W. D., and Beacham, Dan W.: Obst. & Gynec. Surv. **1**: 777, 1946.
2. Beck, Alfred C., and Rosenthal, Alexander H.: Obstetrical Practice, ed. 6, Baltimore, 1955, Williams & Wilkins Company.
3. Charlewood, G. P., and Culiner, A.: J. Obst. & Gynaec. Brit. Emp. **62**: 555, 1955.
4. Cross, J. B., Lester, W. M., and McCain, J. R.: AM. J. OBST. & GYNEC. **62**: 303, 1951.
5. Greenhill, J. P.: Obstetrics, ed. 11, Philadelphia, 1955, W. B. Saunders Company.
6. Kerr, J. M. M., and Moir, J. C.: Operative Obstetrics, ed. 5, London, 1949, Baillière, Tindall & Cox.
7. King, Gordon: AM. J. OBST. & GYNEC. **67**: 712, 1954.
8. Titus, P., and Willson, J. R.: The Management of Obstetric Difficulties, ed. 5, St. Louis, 1955, The C. V. Mosby Company.
9. Ware, H. Hudnall, Jr.: AM. J. OBST. & GYNEC. **55**: 561, 1948.
10. Weintraub, Morris, and Weintraub, David: Am. J. Surg. **54**: 747, 1941.

CARBOHYDRATE METABOLISM IN PREGNANCY*

Observations on Glucagon (Hyperglycemic-glycogenolytic Factor) in Normal Pregnancy and the Puerperium

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MURLIN and his co-workers[12] in 1923 observed that at least two physiologically active fractions were present in aqueous extracts of pancreas, one fraction causing hypoglycemia and the other increasing blood sugar concentration. The hyperglycemic factor was called "glucagon" and could be recovered as a contaminant from certain commercial insulin preparations.[10] Glucagon is also present in the gastric mucosa of dogs and rabbits but is either absent or present in only trace amounts in the stomach and small bowel of swine, sheep, and cattle.[19] Various physiological studies have shown that glucagon is elaborated by alloxan-resistant pancreatic tissue,[6] presumably the alpha cells,[7] although injury to these cells by cobalt salts does not affect the hyperglycemic activity of canine pancreatic extracts.[8] Glucagon is believed to exert its hyperglycemic effect by promoting hepatic glycogen breakdown through activation of liver phosphorylase.[20] In this respect its activity resembles that of epinephrine, but glucagon is not believed to affect glycogenolysis in muscle; hyperglycemia from glucagon administration does not follow in the hepatectomized animal[14] and blood lactate[21] and pyruvate[11] of peripheral blood are not increased by it. These observations are interpreted as evidence against activity of glucagon on skeletal muscle.

The chemical isolation of glucagon by Staub and the Lilly Research group led to increasing availability of highly purified hyperglycemic principle and to stimulation of interest in its metabolic activity.[14, 15] The precise role of glucagon in the utilization of carbohydrate and the regulation of blood sugar is not yet clear. Nevertheless, because of its apparent activity in effecting hepatic glycogenolysis, and in view of the uncertain status of liver glycogen reserves in gestation, it was of interest to study glycogen mobilization with the hyperglycemic factor.

Experimental Methods and Observations

The pregnant patients selected for study were all clinically normal. The stage of pregnancy was between 36 weeks and term. The postpartum subjects were also in apparent good health after uncomplicated pregnancies and

*This investigation was supported by Research Grant H-2166 from the National Heart Institute of the National Institutes of Health, Public Health Service.

delivery. They were studied on the fourth or fifth postpartum day. Twenty nonpregnant volunteers served as controls.

Glucagon,* in a dose of 0.02 mg. per kilogram of body weight, was diluted to a total volume of 10 ml. with 0.9 per cent sodium chloride solution and rapidly administered by vein. All subjects were fasted approximately 15 hours before testing and were under basal conditions. In addition to a pretest blood sample, venous blood was obtained without stasis at 5, 10, 20, 40, and 60 minutes following glucagon injection. Heparin (Connaught) was used as anticoagulant.

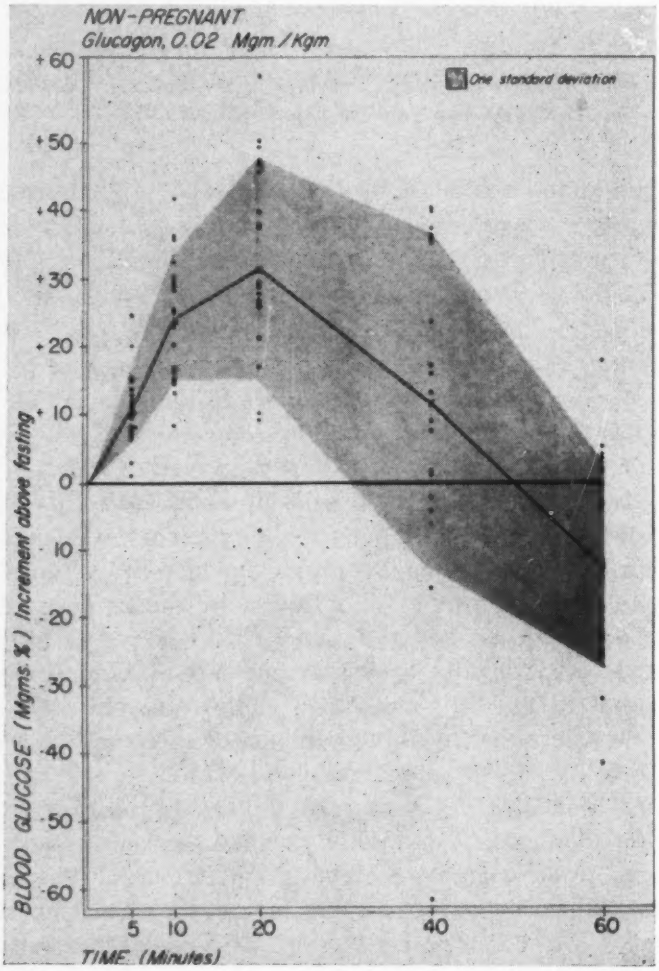

Fig. 1.—Hyperglycemic response to glucagon, 0.02 mg. per kilogram of body weight, for normal nonpregnant subjects. Note hypoglycemic tendency at one hour.

Blood sugar concentration was estimated on zinc sulfate: sodium hydroxide filtrates by the Somogyi-Nelson[13, 17] colorimetric technique. Inorganic phosphorus was determined on 10 per cent trichloroacetic acid filtrates of plasma aliquots with the technique of Fiske and Subbarow.[5] The data obtained were plotted in terms of glucose or phosphorus increments (Δ G, Δ P) during the period of observation and the mean values tested for significance by application of Fisher's "t" test.

*This material was supplied by Dr. W. R. Kirtley, Clinical Research Division, Lilly Research Laboratories, Indianapolis, Ind.

The data for normal nonpregnant subjects are plotted in Fig. 1. Increments in blood glucose from fasting values are shown. Maximum hyperglycemia appeared at the 20 minute interval following injection, and for these subjects was 31.4 ± 16.4 mg. per cent. During the ensuing 40 minutes of the test the blood sugar concentration decreased, and at one hour hypoglycemic levels below the initial fasting values were almost consistently observed. The mean value at 1 hour was –12.5 ± 15.5 mg. per cent.

In contrast with these control observations, values for pregnant subjects between 36 weeks and term are shown in Fig. 2. Although the initial hyperglycemic response for these patients was similar to that of the controls, the

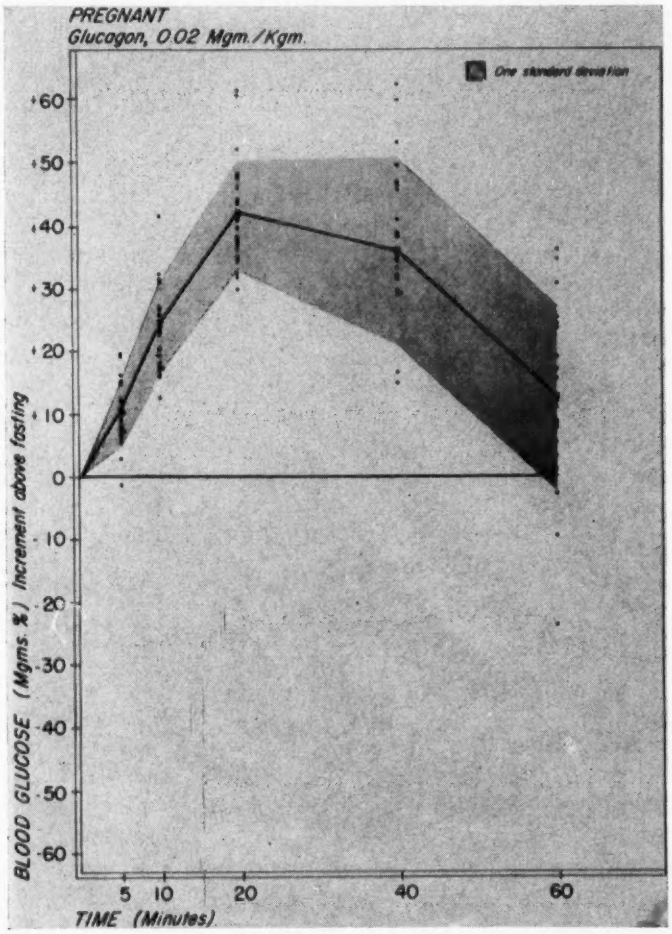

Fig. 2.—Increments in blood glucose concentration above fasting levels for pregnant subjects between 36 weeks and term. Glucagon, 0.02 mg. per kilogram of body weight.

maximum value attained at 20 minutes was somewhat higher (41.8 ± 8.7 mg. per cent). Of particular interest, however, was the tendency to persistence of the hyperglycemia at 40 and 60 minutes. Values below initial fasting levels were encountered in only 3 subjects, in contrast to the hypoglycemic tendency exhibited by the controls. At one hour the observed mean was 12.7 ± 14.6 mg. per cent. By Fisher's "t" test the differences in the means for pregnant and nonpregnant subjects were found to be highly significant.

The postpartum data shown in Fig. 3 resembled the values obtained in pregnancy, but considerably greater variance was observed in the degree of

hyperglycemia attained. The 20 minute maximum of 42.8 ± 15.6 mg. per cent was followed by a decrease to 3.6 ± 22 mg. per cent at one hour. Initially, the hyperglycemic reaction as graphically shown in Fig. 3 was similar to that for control and pregnant subjects. This is also seen in Fig. 4 in which the means for each group are plotted. Mean values and standard deviations for each subject category are given in Table I.

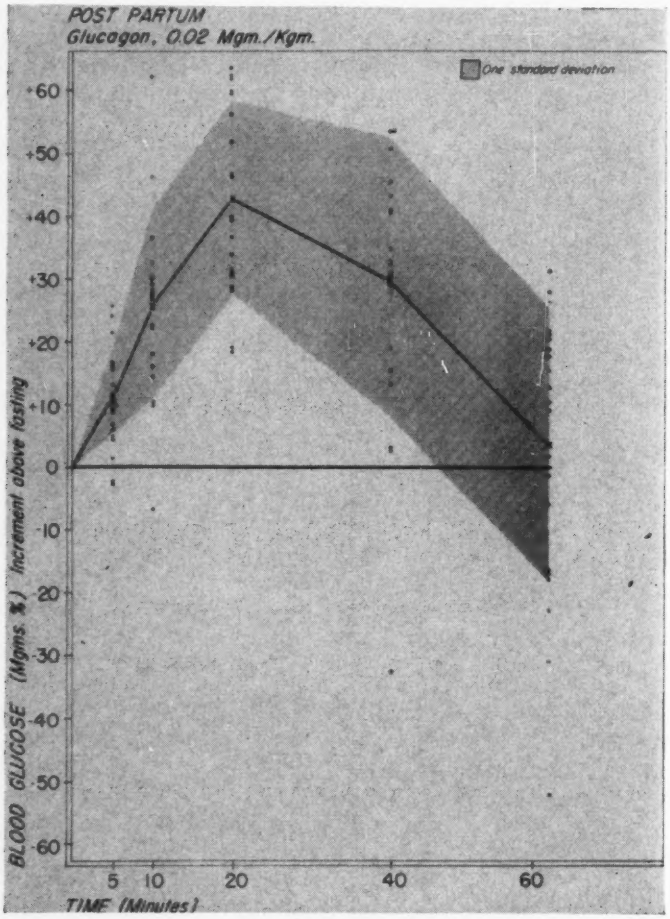

Fig. 3.—Glucagon-induced hyperglycemia in subjects tested on the fourth or fifth postpartum day.

TABLE I. MEAN VALUES FOR INCREMENTS IN BLOOD SUGAR CONCENTRATION ABOVE FASTING LEVELS (Δ GLUCOSE), FOR 20 NONPREGNANT, 20 PREGNANT, AND 20 POSTPARTUM SUBJECTS

TIME AFTER INJECTION (MINUTES)	NONPREGNANT		PREGNANT		POSTPARTUM	
	GLUCOSE (MG. %)	S. D.	GLUCOSE (MG. %)	S. D.	GLUCOSE (MG. %)	S. D.
5	+10.7	± 5.4	+10.0	± 5.2	+11.2	± 8.1
10	+24.0	± 9.2	+23.3	± 7.0	+25.8	±15.1
20	+31.4	±16.4	+41.8	± 8.7	+42.8	±15.6
40	+11.6	±24.9	+35.8	±14.8	+30.2	±22.3
60	−12.5	±15.5	+12.7	±14.6	+ 3.6	±22.0

The depression of inorganic phosphorus associated with the glucagon-induced hyperglycemia is shown in Fig. 5. Attention is directed to the lessened decrease of phosphorus for pregnant and postpartum subjects, contrasting with the data for controls. Although considerable variance was observed

in the data for each group of subjects, the individual tendency to attenuation of phosphorus depression was consistent in the pregnant and puerperal subjects.

Comment

The data presented permit the interpretation that hepatic mobilization of glycogen is not adversely affected by pregnancy. This is indicated not only by the close correspondence of the blood glucose curves during the first 10 minutes of the test for each group of subjects studied, but also by the degree of hyperglycemia attained in pregnancy (Fig. 4). In fact, the hyperglycemic responses observed in pregnant and postpartum subjects tended to

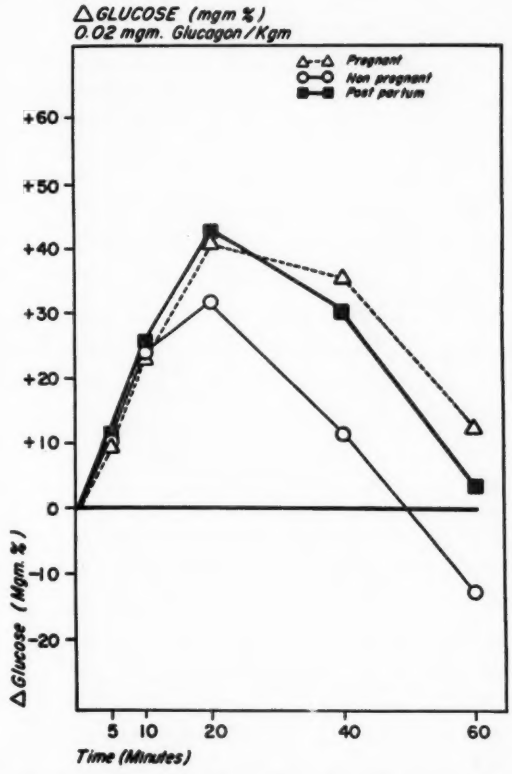

Fig. 4.—Mean values for increments in blood glucose from fasting concentration.

be greater than those of most of the controls, although the variance in the data at the 20 minute interval lessens the statistical significance of this observation. Although these data afford no direct quantitative evidence concerning hepatic glycogen stores, they appear not to support the view of earlier workers that the liver in pregnancy is deficient in glycogen. Preliminary observations of blood glucose responses to repeated administration of glucagon 20 minutes following the initial injection indicate that glycogen mobilization is practically complete at a dosage of 0.02 mg. per kilogram, inasmuch as secondary increases in blood sugar were insignificant. Thus, the hyperglycemia observed under our experimental conditions indicates that the hepatic glycogen reserves in pregnancy and the puerperium are at least equal to, if not greater than, in the nonpregnant state.

These interpretations of our data are consistent with unpublished observations[3] on glycogen synthesis and storage in the rat, showing small but significantly greater liver glycogen reserves in the fasting pregnant animal and comparable glycogen synthetic activity from glucose in pregnant and control animals. Campbell and Kosterlitz[4] have reported hepatic glycopenia in the pregnant rat, and Schmidt and associates[16] observed a similar gestational decrease in the dog. In view of our findings these data are difficult to interpret and they are at variance with the observations of Ingerslev and Teilum,[9] who found no evidence of decreased glycogen in human liver biopsy material.

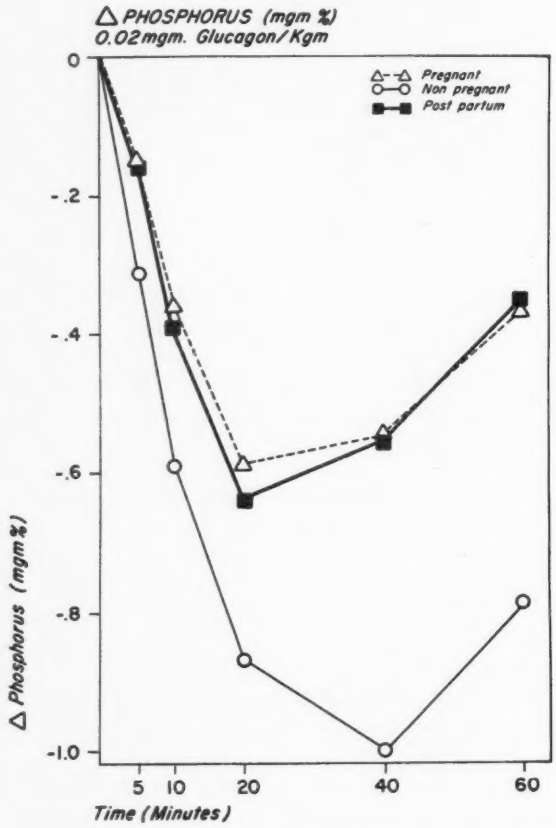

Fig. 5.—Data for plasma inorganic phosphorus after glucagon administration, 0.02 mg. per kilogram of body weight. Decreased response is shown for pregnant and postpartum subjects.

Indirectly our observations suggest that hepatic phosphorylase activation as affected by glucagon according to Sutherland's[20] view is not significantly altered by pregnancy or the hormonal influences of gestation. This is of some interest as it bears not only on our data showing increments in liver glycogen in the pregnant rat but also on Walaas'[22] observations showing increased glycogen storage with estrogen administration. Factors other than changes in phosphorylase activation may account for such increases in glycogen, but our

data in no way indicate the nature of these changes and actual alterations in phosphorylase activation tending to conserve glycogen reserves may have escaped detection by our experimental methods.

A particularly interesting item for speculation is the hypoglycemic "rebound" appearing in the data for nonpregnant subjects but generally absent or attenuated in pregnancy. One possible interpretation of this is that the hypoglycemia is a simple reflection of insulin secretion and/or sensitivity in response to the glucagon-induced hyperglycemia. We[2] have shown previously that insulin resistance develops in late pregnancy, insulin sensitivity being rather remarkably decreased. The significantly higher blood sugar values at one hour in pregnant subjects accordingly are interpreted as secondary to relative insulin resistance with loss of hypoglycemic rebound noted in control subjects. It is considered likely that the higher blood glucose maxima and higher curves for pregnant and postpartum groups between 20 and 60 minutes have a similar basis.

In the early puerperium considerable variance was found in the blood glucose data, although in general they resembled those for pregnancy. Similar variance has been noted for insulin sensitivity,[2] glucose tolerance,[1] fructose utilization,[3] and inorganic phosphorus data in postpartum subjects. It appears that there is considerable individual difference in recovery rates from the gestational changes in carbohydrate metabolism, and that reversion to nonpregnant status is incomplete in many patients by the fourth or fifth day following delivery.

In previous reports[1, 2] it has been shown that the fall in inorganic phosphorus after glucose loading or insulin administration is decreased in pregnancy. This has been interpreted as reflecting an alteration in the peripheral utilization of glucose, possibly at the hexokinase level, secondary to the hormonal changes of gestation. This attenuation of inorganic phosphate response also appears in the glucagon data (Fig. 5), the fall in phosphorus in control subjects contrasting sharply with that in pregnant and postpartum patients. In these experiments, the glucagon-induced hyperglycemia appears to result in phosphate depression in a manner similar to that observed with parenteral glucose administration, although the glucose appearing in the peripheral blood is of hepatic origin. If, as we believe, hepatic glycogen reserves are almost completely mobilized by 0.02 mg. glucagon per kilogram of body weight, and glycogenesis is minimal, the attenuation in inorganic phosphorus depression, with comparable hyperglycemic responses, would appear to reflect changes in peripheral utilization of glucose rather than diversion of glucose to the glycogen depleted liver.[1] This view is further substantiated by the fact that the difference in phosphorus fall appears early when glycogen breakdown is believed to be at its maximum rate. An alternative possibility is that differences in phosphorylase activity occur in the liver in pregnancy and that the glycogen to glucose conversion rate via glucose-6-phosphate results in greater phosphate release, thus maintaining higher levels of

phosphorus in the peripheral blood. This possibility is considered unlikely in view of comparable initial hyperglycemic responses in the three groups of subjects studied.

Summary

1. The hyperglycemic response to glucagon was studied in pregnant, postpartum, and nonpregnant subjects. Comparable hyperglycemia was found for each group. It is believed that glycogen mobilization by glucagon is unaffected by pregnancy.

2. Failure to observe significant hypoglycemia in pregnant subjects following the glucagon-induced increase in blood glucose is interpreted as secondary to insulin resistance developing in late pregnancy.

3. Attenuation of falls in inorganic phosphorus in late pregnancy and the early puerperium which are associated with the hyperglycemia as experimentally induced is interpreted as reflecting a gestational change in the peripheral utilization of glucose.

4. The data fail to indicate a deficiency of hepatic glycogen in human pregnancy.

References

1. Burt, R. L.: Obst. & Gynec. **4**: 58, 1954.
2. Burt, R. L.: Obst. & Gynec. **7**: 658, 1956.
3. Burt, R. L., and Kimel, C. A.: Am. J. Obst. & Gynec. **74**: 295, 1957.
4. Campbell, R. M., and Kosterlitz, H. W.: J. Endocrinol. **6**: 171, 1949.
5. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**: 375, 1925.
6. Foa, P. P., Weinstein, H. R., and Smith, J. A.: Am. J. Physiol. **157**: 197, 1949.
7. Fodden, J. H., and Read, W. O.: Endocrinology **54**: 303, 1954.
8. Goldner, M. G., Volk, B. W., and Lazarus, S. S.: J. Clin. Endocrinol. **54**: 184, 1954.
9. Ingerslev, M., and Teilum, G.: Acta obst. et gynec. scandinav. **25**: 352, 1945.
10. Kimball, C. P., and Murlin, J. R.: J. Biol. Chem. **58**: 337, 1923.
11. Kirtley, W. R., Waife, S. O., Helmer, O. M., and Peck, F. B.: Diabetes **2**: 345, 1953.
12. Murlin, J. R., Clough, H. D., Gibbs, C. B. F., and Stokes, A. M.: J. Biol. Chem. **56**: 253, 1923.
13. Nelson, N.: J. Biol. Chem. **153**: 375, 1944.
14. Pincus, I. J., and Rutman, J. Z.: A. M. A. Arch. Int. Med. **92**: 666, 1953.
15. Pincus, I. J., and Snedecor, J. G.: Metabolism **5**: 150, 1956.
16. Schmidt, H. R., Bickenbach, W., and Jonen, P.: Ztschr. Geburtsh. u. Gynäk. **91**: 527, 1927.
17. Somogyi, M.: J. Biol. Chem. **86**: 655, 1930.
18. Staub, A., Sinn, L., and Behrens, O. K.: Science **117**: 628, 1953.
19. Sutherland, E. W., and deDuve, D.: J. Biol. Chem. **175**: 663, 1948.
20. Sutherland, E. W., and Cori, C. F.: J. Biol. Chem. **188**: 531, 1951.
21. Sutherland, E. W.: Ann. New York Acad. Sc. **54**: 693, 1951.
22. Walaas, O.: Acta endocrinol. **10**: 193, 1952.

A BIOCHEMICAL STUDY OF THE CERVICAL AND NASAL MUCUS FERN PHENOMENON

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IN 1945 Papanicolaou[1] discovered the interesting phenomenon that cervical mucus spread on a slide and left to dry crystallized with "arborization," a fern- or palm leaf-like reaction. He considered this phenomenon characteristic of the time of ovulation. Subsequently numerous workers[2-5] and others carried the investigations further. They concluded that while arborization of the cervical mucus was a reflection of estrogenic activity, the corpus luteum phase was characterized by the disappearance of arborization and the appearance of a cellular reaction (cellular pattern).

This phenomenon was consequently made use of as a test for ovulation, early pregnancy, and in addition, as a means of differentiation between amenorrhea of pregnancy and that from other causes.

Zondek,[6] in 1954, found in his basic study of the phenomenon of the mucus arborization, that other mucus-secreting surfaces in the body (nose, salivary and lacrimal glands, etc.) also produced the reaction. But he considered the phenomenon to be of specific significance only in the cervix where fern formation paralleled estrogenic activity. Further, Zondek and Landerstrom-Lang cooperating with Rydberg[7] showed that the fern phenomenon was dependent upon certain electrolytes, such as sodium and potassium chlorides and potassium bromide in combination with protein substances or saccharides.

Other electrolytes, however, such as calcium and barium chlorides, sodium bromide and sulfate, and potassium nitrate, failed to induce the reaction in Zondek's experiments.

The purpose of this paper is to present a study of the biochemical basis of the phenomenon of arborization demonstrating how it depends upon electrolyte concentration in any solution.

Material and Method

Six sodium salts (chloride, iodide, carbonate, bromide, hydroxide, and sulfate), three potassium salts (chloride, hydroxide, and nitrate), the chlorides of calcium, barium, zinc, and magnesium, silver nitrate and copper

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TABLE I. "SALT CRYSTALLIZATION PATTERN IN AQUEOUS SOLUTION"

AQUEOUS SALT SOLUTION	HIGHER CONCENTRATIONS (ABOVE 1%) WHERE FERN PHENOMENON INDUCED									LOWER CONCENTRATIONS (BELOW 1%) WHERE FERN PHENOMENON INDUCED								
	5%	4.5%	4%	3.5%	3%	2.5%	2%	1.5%	1%	0.5%	0.45%	0.4%	0.35%	0.3%	0.25%	0.2%	0.15%	0.1%
Sodium chloride	A*		A	A	A	F*	A				A	A		A		A	A	
Sodium iodide							F	A	F	A								
Sodium carbonate								A	F	A			A	A				
Sodium bromide					F			A	A			A						A
Sodium hydroxide		F	F	F	F	F	F	F	F	A	A			A		A		
Sodium sulfate		F				F									A	A	A	
Potassium chloride				F		F	F	A		A	A	A	A					
Potassium hydroxide	F	A	A	A						A	A	A						
Potassium nitrate	F	F	F	F		F			F	A			A		A			
Calcium chloride				F			F	F					A					
Barium chloride	F			F				F		A		A						
Zinc chloride							F	F	F	A	A					A		
Magnesium chloride	A	A						F		A		A						
Silver nitrate						F				A		A						
Copper sulfate			F		F				A	A								

*A, Atypical fern pattern.
F, Typical fern pattern.

sulfate, were used. From a 5 per cent salt solution, seventeen further dilutions were made by pipetting measured volumes of salt solutions and distilled water into small sample bottles and mixing thoroughly. In this way, dilutions were obtained up to 0.1 per cent (5, 4.5, 4, 3.5, 3, 2.5, 2, 1.5, 1, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.1 per cent). Measured quantities from the salt solutions were then transferred onto the slides with the use of clean glass rods to spread the drops. The spread drops were left to dry on a warm surface and were then examined under the microscope.

Aqueous solutions (1 per cent) were prepared from the powdered form of a variety of protein substances (peptone, decomposed peptone, dipeptides, tripeptides, polypeptides, serum albumin, gamma globulin, and fibrinogen) and saccharides (fructose, glucose, mannose, and galactose).

Admixtures of a salt and a protein or a salt and a saccharide were made on the slide by using pipettes to transfer a measured volume of each. The two drops were then admixed by means of a fresh glass rod.

External Factors Which Influenced Crystallization.—Variations in crystallization patterns produced by the same salt solution were noted to occur frequently. For while a drop from one solution spread in a circle of 1 cm. diameter gave a certain reaction, another slide from the same solution prepared apparently in a similar manner gave a dense crust of imperfect crystals. Also, a field showing the fern reaction from a solution of a deliquescent salt such as calcium chloride was difficult to maintain and when reheated produced circular disks and columns of crystals. Further, when an admixture was made of two salt solutions, a pattern differing from that of either salt was obtained.

In view of these observations, investigations were carried further and resulted in the following conclusions:

a. Cleaning of slides: Detergents, alcohol, ether, soaps, and cleaning solution (potassium dichromate in sulfuric acid) were all tried separately and in sequence. The cleaning solution gave the best possible result. This was judged not only by the readily spreading drops of distilled water on the slide, a factor frequently shared by the other agents, but more important by the smooth, even spread of the drop from the salt solution itself. Even this method frequently had to be repeated one or more times to avoid the salty drop being divided as it spread and thus producing a dense crust or large, fused, dark-appearing crystals.

b. Leveling of specimen: The slide had to be maintained on a level surface for the sake of uniformity of concentration in the spread drop.

c. Diameter of drop: The drop was spread in a circle of 2 cm. in diameter.

d. Depth of drop: A field more than 1 or 2 mm. in depth produced superimposed patterns which rendered the topmost layer somewhat blurred.

e. Humidity: It was difficult to maintain arborization in the case of a deliquescent salt.

f. Type and rate of evaporation: A rapid heating produced dense masses of material unsuitable for study. Conversely, a warm surface or room temperature in summertime gave a uniform pattern for a proper study.

Results

I. Crystallization Patterns From Aqueous Solutions.—While it was noticed that at each dilution the pattern became basically different, crystallization from aqueous solution generally displayed itself in one or more of four major patterns.

Fig. 1.

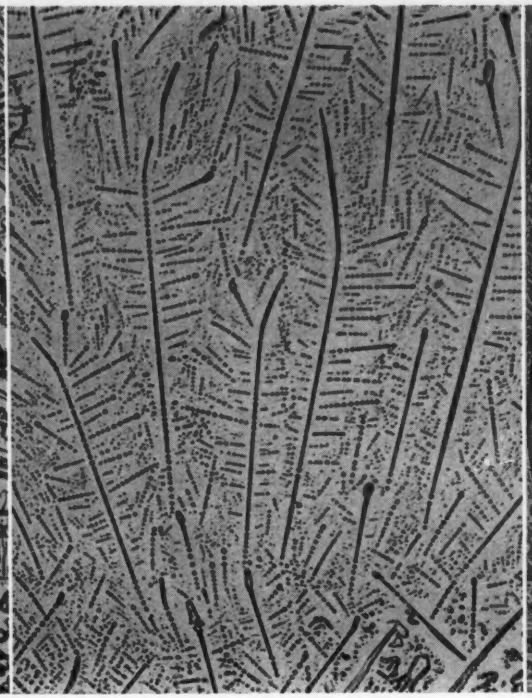

Fig. 2

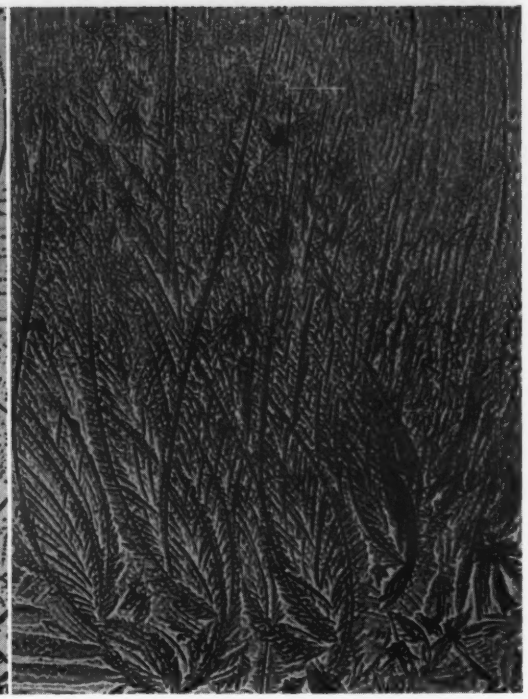

Fig. 3.

Fig. 1.—Sodium chloride solution, 1.25 per cent (aqueous), showing fully formed side branches.

Fig. 2.—Potassium chloride solution, 1.5 per cent (aqueous), showing one phase in the development of fern arborization. The side branches show the unfused crystal nuclei.

Fig. 3.—Sodium carbonate solution, 1 per cent (aqueous), showing palm leaf-like arborization.

1. Large crystals: Rhomboids, rectangles, cuboids, etc., formed, as a rule, in higher salt concentrations (5 to 1.5 per cent in this experiment).

2. Fancy designs: Designs such as venated leaves, candlesticks, phalanges, etc., also formed mainly in higher concentrations.

3. Microcrystals: These were seen in all dilutions; they dominated the field only in low salt concentrations (0.5 to 0.1 per cent). Sodium chloride, however, was an exception at 0.9 per cent.

4. Fern- or palm leaf-like reaction: This reaction was found to form in higher salt concentrations (3.5 to 1.5 per cent), then disappeared, only to reappear in lower salt concentrations (0.5 to 0.25 per cent).

It was noticed, however, that the arborization reaction obtained at concentrations above 1 per cent was comparable to a typical regular fully formed fern, while the fern reactions forming below concentrations of 1 per cent were commonly the atypical, particularly the beaded or pearly pattern. To avoid confusion, the typical form is referred to by the letter *F*. On the other hand, fern structures in patterns like a tree, a bush, an arrow, a spearhead, Y-shape, or starfish in outline, or in compound radiating units, or carrying curved branches, or pearly and beaded in character, etc., are referred to by the letter *A* (Table I).

Fig. 4.

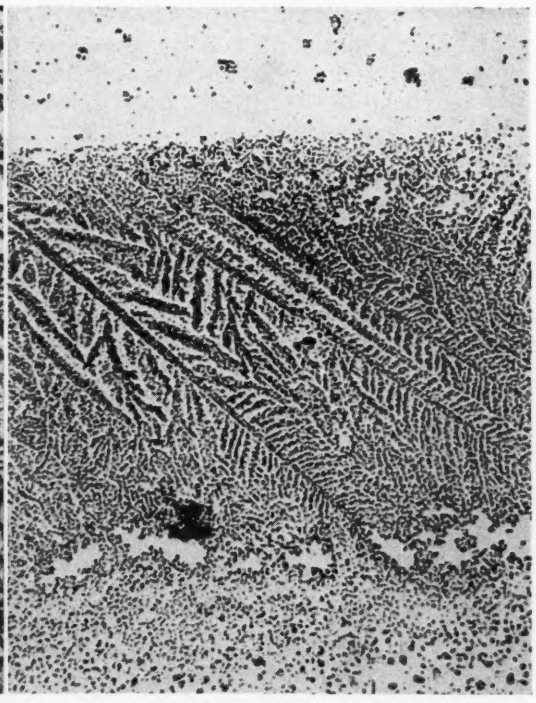

Fig. 5.

Fig. 4.—Barium chloride solution, 1.5 per cent (aqueous), showing pinelike arborization.
Fig. 5.—Barium chloride solution, 0.6 per cent (aqueous), showing the pearly or beaded type of fern arborization, type "A." Crystal nuclei are plentiful.

It was also found that the way the phenomenon was brought about was simply by the arrangement of the crystals sidewise and lengthwise. These crystals might be large, medium, or small in size.

II. Types of Fern Pattern.—It was of interest to note that chemical ferns differed in appearance with the different salt solutions; for it was seen that

while 1.25 per cent sodium chloride solution gave a pattern of long poles carrying perpendicular side branches (Fig. 1), 1.5 per cent potassium chloride gave a different pattern of arborization like bent needles (Fig. 2), and 1 per cent sodium carbonate solution gave a third pattern of palm leaves-like branching (Fig. 3). Further, the same salt gave varied patterns of fern structures in the different concentrations where the reaction appeared. As an illustration of this, we find that while barium chloride solution in 1.5 per cent concentration gave the pattern of pinelike branching (Fig. 4), it gave a featherlike pattern in 0.6 per cent solution (Fig. 5).

When crystal formation or disintegration was observed microscopically, its component parts appeared as minute circular disks which coalesced or dispersed, respectively. The fern reaction behaved in a similar manner. The smear taken from the 1.5 per cent potassium chloride solution demonstrates that the crystals forming the stem have fused in part, whereas those building the branches are still discrete nuclei (Fig. 2). On the other hand, with further dilution a fern can be seen to break up into its components, and the field becomes simply overwhelmed with minute crystals. These minute crystals, although present in all smears in varying amounts, dominated the field only in concentrations below 1 per cent with all the salt solutions. Sodium chloride solution in a concentration of 0.9 per cent constitutes a good illustration (Fig. 6).

III. Crystallization Patterns of Salts When Admixed With Organic Substances.—Each of the fifteen salts in its sequential series of dilutions was tested with one or more of the 1 per cent protein solutions. It was found that only in certain proportions and only in certain dilutions did the dried mixture of the two substances produce the palm-leaf or fern reaction. The admixture of salt and protein gave a positive result only when the resultant strength of the salt solution was brought to a level where the salt alone gave the reaction (Table II).

TABLE II. CRYSTALLIZATION FROM SALT AND PROTEIN ADMIXTURES

SALT	STRENGTH IN ORIGINAL AQUEOUS SOLUTION (%)	PROTEIN USED	STRENGTH OF PROTEIN SOLUTION (%)	AMOUNTS OF BOTH SUBSTANCES USED IN THE ADMIXTURE, SALT SOLUTION PLUS PROTEIN SOLUTION (C.C.)	RESULTANT STRENGTH OF SALT IN THE ADMIXTURE (%)	REACTION
Sodium chloride	3	Gamma globulin	1	0.03 + 0.01	2.25	Negative
	5	Gamma globulin	1	0.01 + 0.01	2.5	Positive
Sodium iodide	4	Peptone decomposed	1	0.03 + 0.01	3	Negative
	4	Peptone decomposed	1	0.01 + 0.01	2	Positive
Sodium bromide	4	Globulin	1	0.01 + 0.01	2	Negative
	4	Globulin	1	0.01 + 0.03	1	Positive
Sodium sulfate	4.78	Peptone	1	0.01 + 0.01	2.4	Negative
Potassium nitrate	2.5	Polypeptides	1	0.05 + 0.01	2	Negative
	4	Polypeptides	1	0.01 + 0.03	1	Positive
Barium chloride	4.5	Fibrinogen	1	0.12 + 0.01	2.5	Negative
	4.5	Fibrinogen	1	0.01 + 0.02	1.5	Positive

Again by application of the same method as with protein solutions to produce a series of admixtures of salt and saccharide solutions, a similar result was obtained (Table III).

IV. Crystallization Patterns and Molarity.—The crystallization pattern produced by a salt in a certain concentration was found to match the pattern

produced by another salt in a different concentration, when both solutions contained the same number of molecules and conditions were substantially constant. Thus, the crystal pattern produced by the 1.75 per cent sodium

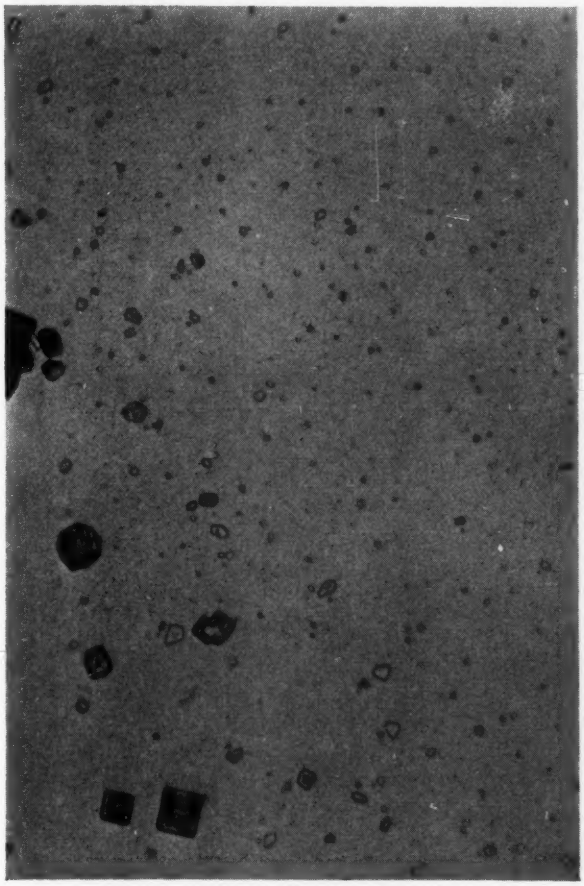

Fig. 6.—Sodium chloride solution, 0.9 per cent (aqueous), showing crystal nuclei.

TABLE III. CRYSTALLIZATION FROM SALT AND SACCHARIDE ADMIXTURES

SALT	STRENGTH IN ORIGINAL AQUEOUS SOLUTION (%)	SACCHARIDE USED	STRENGTH OF SACCHARIDE SOLUTION (%)	AMOUNTS OF BOTH SUBSTANCES USED IN THE ADMIXTURE, SALT SOLUTION PLUS SACCHARIDE SOLUTION (C.C.)	RESULTANT STRENGTH OF SALT IN THE ADMIXTURE (%)	REACTION
Sodium chloride	1.75	Fructose	1	0.03 + 0.01	1.3	Negative
	3	Fructose	1	0.03 + 0.01	1.3	Negative
	4	Fructose	1	0.01 + 0.01	2	Positive
Sodium bromide	1	Glucose	1	0.01 + 0.01	0.5	Negative
	4	Glucose	1	0.01 + 0.01	2	Negative
	2	Glucose	1	0.01 + 0.01	1	Positive
Potassium chloride	1	Mannose	1	0.01 + 0.01	0.5	Positive
Potassium nitrate	1	Galactose	1	0.05 + 0.01	0.8	Negative
	2.5	Galactose	1	0.05 + 0.01	2	Negative
	1	Galactose	1	0.01 + 0.01	0.5	Positive

Fig. 7. Fig. 8. Fig. 9.

Fig. 7.—A smear taken from the mixed mucus sample immediately after collection. It shows the bushy type of arborization.
Fig. 8.—A smear taken from the same sample after being dehydrated, then made into solution. The character of arborization changed to the ferny type.
Fig. 9.—Smear taken from ashed mucus after it was dissolved in 1 c.c. distilled water. It shows the fern reaction (cf. Fig. 1).

chloride solution closely matched that of sodium carbonate solution in a concentration of 3.17 per cent and that of sodium sulfate solution in a concentration of 4.25 per cent, etc.

V. Crystallization Patterns in a Nasal Mucus Sample Before and After Ashing.—Last, it became inevitable to apply the above chemical facts to the biological secretions. Mucus secretion from any organ in the body, under normal circumstances, is simply a lymph transudate containing electrolytes similar to those found in the blood, but in different concentrations. For this reason, as well as the time factor involved, the nasal mucus was considered the most suitable for the biochemical test.

Testing a smear from a sample of nasal mucus in the fresh state and after all organic matter had been eliminated was contemplated. Nasal mucus was collected from more than one subject to obtain a reasonable quantity.

Six normal women volunteers in the first half of the cycle were chosen. Each blew her nose once into a beaker and about 1 c.c. of mucus was thus collected. A smear was taken from this mixed sample. It showed the fern pattern. The mixed sample was then placed in an electric oven at 100° C. for 20 minutes. The dried material was next washed down the sides of the beaker with 2 c.c. distilled water by means of a pipette. By a rocking movement the dried mucus was brought into solution. A smear taken from this solution showed the fern pattern. This is suggestive that the salt or salts responsible for the fern phenomenon were water soluble. An additional 2 c.c. of distilled water was then added and the solution was transferred into a small deep beaker. All organic matter was eliminated by ashing the sample in an electric ashing furnace which was kept at a constant temperature of 550° C. for four hours. The residual ash was then dissolved in 1 c.c. distilled water and the smear taken from this material gave the fern reaction. The ash solution was diluted further by adding another 0.5 c.c. of distilled water. The smear then taken showed, exclusively, the crystal nuclei reaction.

Comparison between the smears, the one taken from the mixed mucus sample immediately after collection, and the other after the same sample was dehydrated and then made into solution with distilled water, shows clearly the role of salt concentration in situ; for while the first smear showed a bush-like pattern (Fig. 7), the second smear showed a more fernlike pattern (Fig. 8). When, however, the mucus was ashed and the ash was then made into solution, the phenomenon was reproduced and, likewise, produced a fern reaction in the first solution (Fig. 9) (cf. Fig. 1). Crystal nuclei reaction resulted when the sample was diluted further.

A preliminary analysis of both the nasal and the cervical mucus showed that they contained sodium in large amount, potassium in smaller amount, and calcium in lesser amount.

Comment

The fact that all the salts gave the fern or palm leaf-like reaction from aqueous solutions demonstrates that the phenomenon of fern crystallization is dependent on salt concentration. The reason this was overlooked in the past is simply because the optimum concentrations for such a reaction were not reached in previous experiments.

Substances such as proteins and/or saccharides acted as a medium which influenced the pattern only in so far as thickness, length, or density, or in short the "crystal habit," was concerned. The type of skeleton or internal

structure was never influenced. Adsorption of a solvent or a material dissolved in it tends to retard deposition upon certain atomic planes.[8] In this way the crystal habit of a given substance may vary markedly without any alteration in its composition. Also, the unconditioned addition of protein or a saccharide to the salt solution failed to give the reaction in some of the smears while it gave it in others. In this study it was shown that even with the addition of a protein substance or a saccharide, respectively, certain optimum concentrations must be reached before the fern phenomenon could be induced. This explains why a certain number of salts failed to give the reaction in Zondek's experiment, while all salts gave the reaction in this experiment. Further, it was noted that the fern reaction induced by a double salt, such as sodium and potassium chlorides in aqueous solution, displayed a pattern different from that produced by either salt solution alone. This is an additional illustration of how the medium influenced the pattern of crystallization externally and not the skeleton or internal structure.

Summary and Conclusions

1. The fern reaction is a phenomenon dependent solely on electrolyte concentration.

2. All salts gave the reaction in aqueous solutions in certain optimum concentrations.

3. The presence of protein and/or saccharide influenced only the external appearance but not the basic skeleton of whatever reaction was induced.

4. When organic material was eliminated by ashing a mucus sample, the fern phenomenon was reproduced.

I should like to express my appreciation to Dr. M. Edward Davis, Professor and Chairman of the Department, for the opportunity of working in his laboratory.

Acknowledgment is also due to Dr. G. L. Wied, Director of the Cytology Laboratory, for his valuable advice and, to I. J. Lichton, Ph.D., for his advice and technical assistance.

References

1. Papanicolaou, G. N.: Anat. Rec. **91**: 293, 1945.
2. Roland, M.: Am. J. Obst. & Gynec. **63**: 81, 1952.
3. Campos da Paz, A.: Trans. Internat. & 4th Am. Congress on Obst. & Gynec. (Supp. vol. Am. J. Obst. & Gynec.) **61A**: 790, 1951.
4. Pommerenke, W. T.: Trans. Am. Gynec. Soc. **69**: 79, 1946.
5. Abarbanel, A. R.: Trans. Am. Soc. Study of Sterility, 1946, p. 46.
6. Zondek, B., and Rozin, S.: Obst. & Gynec. **3**: 463, 1954.
7. Rydberg, E.: Acta obst. et gynec. scandinav. **28**: 172, 1948.
8. Chamot, E. M., and Mason, C. W.: Handbook of Chemical Microscopy, ed. 2, New York, 1938, John Wiley & Son, vol. 1, p. 334.

THE USE OF URECHOLINE IN THE PREVENTION OF POSTPARTUM URINARY RETENTION

Final Report

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THIS paper represents the final report of a study begun in 1952.[1] The preliminary results were encouraging and the investigation was expanded to evaluate fully the significance of the original report.

The incidence of puerperal urinary retention is reported as between 3.8 per cent[2] and 13.8 per cent.[3] Though of no tremendous or disastrous consequences, it can be extremely troublesome and exasperating to patient, doctor, and nurse.

Physiologically, the postpartum bladder is very different from the bladder in the pregnant state. Bennetts and Judd[4] concluded that the postpartum bladder shows greatly diminished muscular tone, decreased sensitivity, and markedly increased capacity.

The etiology of these changes is considered to be partly hormonal. If all puerperal bladders are so affected, however, why do some postpartum patients develop urinary retention and others not? For this answer, everything from anesthesia to type of delivery has been blamed. Divergent views are held as to which factor is the most important. In all probability, several factors, including individual variation in hormone metabolism, play a part in causing and/or prolonging urinary retention during the puerperal period.

It is interesting to note that in *1915* Taussig[2] reported catheterization necessary in 3.8 per cent of his cases, with an operative delivery rate of 11.4 per cent. In recent times, the catheterization rate has almost tripled and the operative delivery rate is some seven times as great (Table I). These data may indicate that operative delivery increases postpartum urinary retention.

Table I. Suggests That Operative Delivery Has Increased Incidence of Catheterization

	Taussig 1915	This Report 1954
Per cent requiring catheterization	3.8	9.7
Operative delivery (%)	11.4	80

Material and Methods

In this study two groups of similar patients were used. Complete records were kept of all patients in both groups. These include length of each stage of labor, amount of analgesia, anesthesia, type of delivery, type of episiotomy, complications of delivery, time from delivery to first micturition, and amount first voided.

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Both groups were under similar catheterization orders, varying from 8 to 12 hours. An effort was made to give the patients in each group every opportunity to void prior to any catheterization.

Urecholine* (the urethane of beta-methylcholine chloride) was given routinely to the "prophylactic group" in an effort to minimize the number of catheterizations. Urecholine has proved effective in combating bladder hypotonicity, which, in effect is the physiological state of the postpartum bladder.[4, 5]

The prophylactic group received an oral dose of 15 mg. of Urecholine upon returning to their rooms after delivery and then every 4 hours for six doses thereafter. On this dosage the incidence of side reactions was nil and at no time did it prove necessary to use the antidote atropine.

Table II shows that the two groups compare well in relation to types of delivery, analgesia, anesthesia, etc.

Results

Table II could be expanded to equal one table for each specific heading.

TABLE II. COMPARISON OF CONTROL AND PROPHYLACTIC GROUPS

	PROPHYLACTIC GROUP 821 PATIENTS	CONTROL GROUP 975 PATIENTS
Average total length of labor	8 hours	8.5 hours
Length of labor 24 hours or more	1.9%	2.0%
Spontaneous delivery	29.3%	27.5%
Operative delivery	70.7%	72.5%
Central episiotomy	54.7%	59.0%
Lateral episiotomy	35.0%	30.5%
Saddle anesthesia	78.9%	74.3%
Routine analgesia*	40.7%	48.6%
Less than routine analgesia	17.9%	16.1%

*Routine analgesia at Mercy Hospital during the period of this study consisted of Seconal, 3 grains (0.2 Gm.) orally, and Demerol, 100 mg. with scopolamine, 0.4 mg. (1/150 grain), given intramuscularly or one half intravenously.

This was done and all variations and differences cross-checked mathematically. Each group was compared with the control. Further complete analysis of the catheterized patients failed to disclose any one etiological factor for postpartum urinary retention. In this analysis of the clinical results, Urecholine, as used in this study, did not decrease the necessity for catheterization, as would have been expected from the preliminary report[1] (Table III).

TABLE III. THE PERCENTAGE OF PATIENTS REQUIRING CATHETERIZATION OR REPEATED CATHETERIZATION IS THE SAME IN BOTH GROUPS

	URECHOLINE PROPHYLACTIC GROUP		CONTROL GROUP	
	NUMBER	%	NUMBER	%
Total No. of patients	821	100	975	100
Catheterized	80	9.7	91	9.3
Not catheterized	741	90.2	884	90.5
Repeat catheterization	17	0.1	27	0.2

TABLE IV. AMOUNT OF RESIDUAL URINE SHOWS NO SIGNIFICANT DIFFERENCE IN THE TWO GROUPS

	URECHOLINE PROPHYLACTIC GROUP	CONTROL GROUP
Number of patients	102	100
Average residual urine	167.4 c.c.	184.1 c.c.

*Merck & Co., Inc., Rahway, N. J., supplied the drug used in this study.

Residual urine checks were made on 100 similar patients in the control and the treated groups. All residual urine samples were obtained 24 hours post partum. Little or no difference in the average residual urine between the two groups could be seen, as shown in Table IV.

One hundred and forty-nine patients received Urecholine only after urinary retention was established. All except 20 per cent of this group received oral treatment. This treatment was successful in preventing the need for catheterization in 40.9 per cent of these patients. The failure rate in this treatment group might have been far less if Urecholine had been used subcutaneously rather than orally.

Conclusions

The prophylactic use of Urecholine, as employed in this study, did not diminish the incidence of catheterization in the postpartum period.

No one etiological factor could be found to account for urinary retention, although operative delivery is felt to increase the incidence post partum.

I wish to express my sincere appreciation and gratitude to Dr. J. J. Erwin, Head of the Department of Obstetrics of Mercy Hospital and to the attending Obstetrical Staff for their cooperation during this study.

To the sisters and nurses of the Obstetrical Department, my sincere thanks for the innumerable catheterizations.

References

1. Fleming, A. R.: Am. J. Obst. & Gynec. 64: 134, 1952.
2. Taussig, F. J.: Tr. Am. Gynec. Soc. 40: 351, 1915.
3. Roll, R. M.: Am. J. Obst. & Gynec. 42: 117, 1941.
4. Bennetts, F. A., and Judd, G. E.: Am. J. Obst. & Gynec. 42: 419, 1941.
5. Lee, L. W.: J. Urol. 64: 157, 1950

THE MOTHERS OF MONGOLOID BABIES: A RETROSPECTIVE APPRAISAL OF THEIR HEALTH DURING PREGNANCY*

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DESPITE the passage of 80 years since Mongolism was identified as a clinical entity, knowledge of its causation remains hazy. Important clues as to the general nature of the condition are not wanting, however.[1] Some of these clues are derived from the study of mothers, others from the study of Mongoloid infants. For example, epidemiologic data demonstrate convincingly that women face increasing risks of having Mongoloid babies as they get older, especially as they near the menopause.[2, 3, 4] The babies themselves are significantly smaller than normal at birth[5] and no matter how prematurely they are born, characteristic deformities of the eyes (Fig. 1, *A*, *B*, and *C*), nasal bones, heart, or little finger are already present. Assuredly the meaning of these stigmas lies in the fact that they are all anomalies of tissues differentiating at about the same time, namely, in the eighth week of pregnancy (Figs. 2 and 3).[1, 6] The combined clinical and epidemiologic observations that have been assembled during the better part of a century point to the operation of maternal factors, in large part chronic, acting during the first trimester of pregnancy, to induce Mongolism as a congenital defect in a potentially normal embryo.[6, 7] Since the mother is her own baby's incubator, so to speak, the present study was undertaken to appraise maternal health, especially during early gestation, of a group of mothers of Mongoloid babies and compare it with that of a control group.

Material and Methods

Obstetric records of all mothers recorded to have given birth to Mongoloid babies during the 20 year period, 1935 through 1954, at the Boston Lying-in Hospital were selected for retrospective study of factors that might throw light on the origin of the condition. Because age enters so clearly into the causation of Mongolism this factor was allowed for as far as possible in assembling age-matched controls. The next mother admitted for delivery who was of the same recorded age as a mother of a Mongoloid baby presently being placed in the study group was selected to go among the controls.

Difficulties of the type inherent in any retrospective study of clinical records were encountered—difficulties stemming primarily from the fact that records used were not specially prepared for the particular analysis to be made. The source records were reasonably satisfactory, however, in providing

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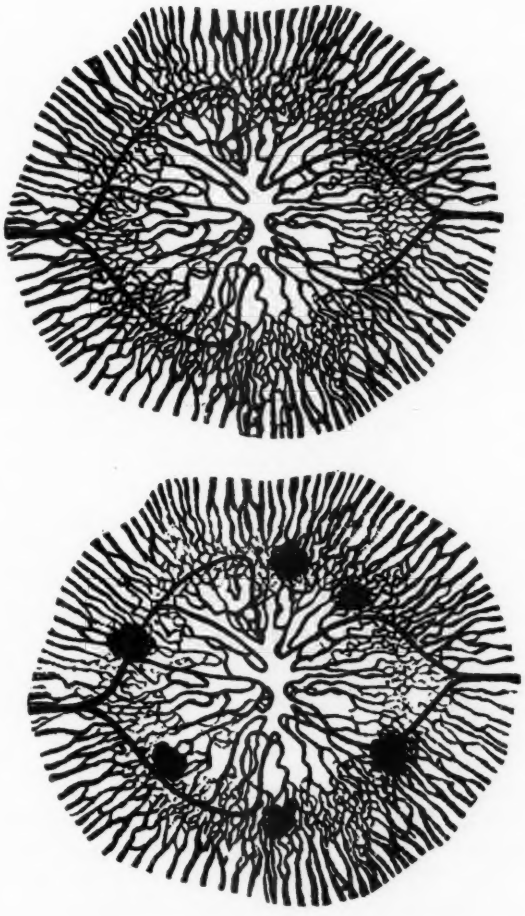
A.

B.



C.

Fig. 1.—*A*, A newborn Mongoloid infant of 8 months' gestational age showing Brushfield spots of the iris and classical appearance at birth.

B, The pupillary membrane at about the eighth week of embryonic age, after Versari.[20]

C, A conjectural scheme to indicate how "Brushfield spots" i.e., "clocklike" concentrations of chromatin in the iris and peripheral hypoplasia could occur following a critical disturbance of differentiating capillaries at about that stage of gestation.

basic data that may be of use in determining the direction of future investigation. Ultimately, if such information is to be given predictive meaning and occurrence reduced, the study of Mongolism must become prospective; success is to be measured by lowered incidence.

Incidence and Prevalence.—The diagnosis of Mongolism was made 52 times during the years 1935 through 1954, an additional 14 having been reported from 1930 to 1934 (Table I). This represents a ratio of 1:928 or a rate of 1.07 per 1,000 births in this hospital. The figure is probably conservative for assuredly some unsuspected cases and even a few suspected cases would not be diagnosed during the brief postpartum period of hospitalization. Øster,[8] in a review of medical literature, found the prevalence to lie between 1:478 and 1:898 births, the average rate being 1.7 cases per 1,000 births; and Kurland[9] puts the figure for Rochester, Minnesota, based on Mayo Clinic experience, at 1.0 per 1,000. When arranged by 5 year intervals, a provocatively interesting rise in the occurrence of Mongolism at the Boston Lying-in Hospital is found from a plateau of about 1 per 1,000 births before and during the years of World War II to 1.5 in the postwar period, with an impressive drop in the years 1950 through 1954.

TABLE I. INCIDENCE OF MONGOLISM, BOSTON LYING-IN HOSPITAL, 1930-1954

YEAR	DELIVERIES	MONGOLOID BABIES BORN	5 YEAR TOTALS	RATE PER 1,000 PREGNANCIES
1930	1,958			
1931	1,956			
1932	2,100			
1933	2,106			
1934	2,457		14*	1.32
1935	2,768	2		
1936	2,698	4		
1937	2,648	2		
1938	2,529	4		
1939	2,641	3	15	1.13
1940	2,749	2		
1941	2,977	4		
1942	3,084	1		
1943	2,623	4		
1944	2,457	2	13	.94
1945	2,206	5		
1946	2,590	2		
1947	2,712	1		
1948	2,302	5		
1949	2,242	5	18	1.50
1950	2,139	2		
1951	2,263	1		
1952	2,377	0		
1953	2,222	0		
1954	2,451	3	6	.56
Total	61,255	52	66	1.07

*Source: Beidleman.[14]

Maternal Age and Birth Order of Babies.—Relatively advanced age of the mothers of Mongoloid babies is again demonstrated in this study. Most births of Mongoloid infants are reported to occur when the mothers are 40 years of age or over, whereas most births in a general population occur when the mothers are nearer 25 years of age. Actually the average age of the mothers of

Mongoloid babies in the series is very nearly 34 years, whereas the mean age of mothers in Massachusetts was 28.5 at the last census, a scant half year more than that of mothers entering the Boston Lying-in Hospital.[10]

The data attest the generally held belief that the order of birth is not of primary importance in the causative complex of Mongolism. The average birth order of the 52 Mongoloid babies is 3.8, very close to that—3.45—of the controls. Others[11] have demonstrated that the significance of the association with a fairly high order of birth is the association with maternal age.

Birth Weight.—The finding of low birth weights of Mongoloid babies in this series harmonizes with the observation of Smith and McKeown[5] that Mongoloid infants are slightly, but significantly, lighter than average at birth. The mean weight of these 52 babies was 6.27 pounds, whereas that of the controls was 7.01 pounds. Smith and McKeown also found Mongoloid babies to weigh almost ¾ of a pound less than controls and concluded that a low birth weight was not wholly explicable as a function of prematurity but "must be attributed in part to a low rate of prenatal growth." Abnormal development before birth is also suggested by Øster's observation that 49 per cent of 347 Mongoloid infants were in poor condition at birth—that is to say, they were lax or cyanotic, if not actually asphyxial.

Fig. 2.—Fetus, apparently 7½ weeks of gestational age, in amniotic sac. (Courtesy of Marjorie E. Jacobson, Millard Fillmore Hospital, Buffalo, N. Y.)

Interval Between Birth of Propositus and Termination of Preceding Pregnancy.—An unusually long interval between the birth of a Mongoloid infant and its immediate predecessor has been reported by several investigators who studied the characteristics of pregnancies resulting in the birth of Mongoloid babies. Long intervals were noted by van de Scheer[12] and Jenkins,[13] and Benda[2] observed that "the most impressive factor of all is the inability to become pregnant which manifested itself in involuntary long intervals between pregnancies." An average time lapse of 4.8 years was determined by Beidleman[14]

in his study of mothers of Mongoloid children. Thalhammer[15] found that 29, or 15 percent, of 196 mothers who had given birth to Mongoloid babies had the baby 10 years or more after the preceding child; this is an impressive fraction of a group of mothers to experience such a long period of childlessness. Such figures are inconclusive, however, unless maternal age is taken into account, since any sizable group of mothers of Mongoloid babies is weighted with older women.

Smith and Record[4] attempted to control the age factor by investigating prenatal characteristics of 252 mothers of Mongoloid babies and as many age-matched mothers who did not bear Mongoloid children. They found the interval differences between 208 of the mothers of Mongoloid babies and 137 of the controls to be insignificant. However, the 34 per cent greater attrition of the control series (due to a less effective tracing of these women) indicates the operation of factors of self-selection that cast serious doubt on utility of the control population, especially since their data show differences between the experiences of younger and of older women which are cancelled out when mothers of differing ages are treated as a single universe.

TABLE II. INTERVAL BETWEEN BIRTH OF MONGOLOID BABY OR CONTROL AND PRECEDING BIRTH, BY TWO AGE GROUPS

	33 YEARS OLD, OR YOUNGER		34 YEARS OLD, OR OLDER	
	INTERVAL TO PRECEDING LIVE BIRTH, STILLBIRTH, OR MISCARRIAGE	INTERVAL TO PRECEDING LIVE BIRTH	INTERVAL TO PRECEDING LIVE BIRTH, STILLBIRTH, OR MISCARRIAGE	INTERVAL TO PRECEDING LIVE BIRTH
Mothers of Mongols	3.0 years	4.5 years	3.6 years	4.9 years
Mothers of comparison group babies	3.0 years	3.0 years	4.3 years	4.5 years

In the present series of 104 mothers the time interval preceding the birth of the propositus and its predecessor is shown in Table II. This table also gives information on the reproductive performance of the two groups of women according to whether they were 33 years of age or younger or 34 years or older. Differences in fertility itself were not observed in the younger women and a longer interval between birth of a Mongoloid infant and a predecessor liveborn sibling could be accounted for by pregnancies resulting in miscarriages. Older women who had given birth to Mongoloid babies are shown to have been actually more fertile than their age-matched controls. Notwithstanding, the interval elapsing between the birth of the Mongoloid child and a liveborn sibling was longer. This was because 12 of 31 older mothers of Mongoloid babies had had miscarriages just prior to the birth of the Mongoloid whereas only 5 of 31 age-matched controls were recorded to have lost the previous baby.

This factor of fecundity coupled with prenatal wastage becomes even more striking when all mothers were compared after exclusion of those who had no previous pregnancy recorded: 17 of 37 (45.9 per cent) multiparous mothers of Mongoloid babies lost the conceptus at the termination of the immediately preceding pregnancy; two of the 17 had had 2 such mishaps; and 2 others a succession of 3 miscarriages. In the comparison group, on the other hand, only 6 of 42 (14.3 per cent) of the multiparous mothers had miscarriages; and none had had 2 or more in succession.

Previous Miscarriages.—Of total pregnancies prior to the birth of the propositi the mothers of Mongoloid babies had 15.5 per cent ending in miscarriages or stillbirths; their controls had only 9.4 per cent. In the younger group aged 33 years and under, 6 of 21 mothers of Mongoloid babies gave a history of prior miscarriages; there was only one such mother among the controls. Among the 31 older mothers of the study group 20 miscarriages had occurred, and only 13 among their controls. It is of interest that 22.1 per cent of multiparous mothers of Mongoloid babies had a history of termination of the first pregnancy by a miscarriage whereas only 10 per cent of the multiparous mothers in the comparison group had such a history.

The implication is clear that mothers who bore Mongoloid babies were facing adverse reproductive risks even before the pregnancies which came under scrutiny got under way. This suggestion is intensified by the greater frequency of first trimester bleeding and of chronic gynecologic and systemic disorders among mothers of Mongoloid babies than among controls.

Fig. 3.—Histologic sections of the hand of the "normal" human embryo at about 6 weeks of embryonic life (left) and at about 7½ weeks of gestational age (right). Note the status of fifth finger development: no segmentation at all has occurred in the specimen on the left. All 3 phalanges are discernible in the specimen on the right. (Courtesy of Dr. Kurt Benirschke, Boston Lying-in Hospital, Boston, Mass.)

First Trimester Bleeding.—Many investigators[2, 13-16] have observed that over 15 per cent of mothers of Mongoloid babies have had vaginal bleeding or spotting during the first trimester of the pregnancy. In the present study 10 (over 20 per cent) were recorded to have had first trimester bleeding whereas only 5 (10 per cent) of the control group had had similar bleeding. When first trimester bleeding is considered by the age of the mothers who bled, 9 of the 10 cases in mothers of Mongoloid babies occurred in women who were 34 years or over, whereas 4 of the 5 cases among the controls occurred

in women 33 years or younger. Thus twice as much first trimester bleeding occurred in mothers of Mongoloid babies as in controls; and it was disproportionately distributed among the older mothers of afflicted children.

Retroversion of the Uterus.—In contrast to the frequent finding of first trimester bleeding in older women who had borne Mongoloid babies, the prevalence of chronic retroversion of the uterus was noticeably higher among the younger mothers of these defective babies. Retroversion had been recorded prior to the proband pregnancy in the protocols in 6 of 21 (nearly 30 per cent) mothers 33 years of age or younger, whereas long-standing retroversions of the uterus had not been previously observed at all in the records of their controls. Long-standing retroversion of the uterus was equally common in older women, both the mothers of Mongoloid babies and their controls (4 of 31 in each group). The significance of the finding is wholly speculative but retroversion might result in a temporary compression-stagnation effect if the gravid uterus gets trapped under the sacrum at the end of the second month of pregnancy just before it is due to enlarge upward into the pelvic brim. When newly discovered as well as long-standing retroversions of the uterus were included, 18 were recorded in 52 mothers of Mongoloid babies. This compared with 11 cases in the 52 controls. The finding harmonizes in principle with Schröder's[16] observation that 26 per cent of 99 mothers of Mongoloid children had significant retroversion of the uterus, in comparison with only 5.5 of 248 mothers grouped for comparison. The subject deserves intensive study.

Organic Heart Disease.—Sixteen (or nearly 30 per cent) of the 52 mothers of Mongoloid babies were referred to the cardiac clinic for consultation because of signs and symptoms of heart disease which caused concern to residents or obstetricians of the prenatal clinic. Chiefly encountered was rheumatic heart disease, although hypertensive and hyperthyroid heart disease was each diagnosed once; and one young mother had severe congenital heart disease with patent ductus and clubbing of digits.

Only 4 (or less than 10 per cent) of the controls were referred to the cardiac clinic. Of these one had minimal hypertensive heart disease, 2 had minimal heart disease of presumed rheumatic etiology, and the fourth had aortic stenosis and mitral insufficiency with a past history of streptococcal disease. She, parenthetically, gave birth to a baby with cleft palate.

Thus there was four times as much organic heart disease in mothers of Mongoloid babies as in their age-matched controls. No differences were noted in the two age groups studied except that organic heart disease, and this was to be expected, was far more frequent in older women—in both the study group and controls.

Comment

For many years it has been known that older women are more prone to bear Mongoloid children than are younger women; and in England the risk of producing a Mongoloid child has been demonstrated to increase about fifty or one hundred fold from around 0.3 per 1,000 pregnancies in the twenties to 15 and higher in the forties. This is probably the most striking epidemiologic constant that has been unearthed about any of the congenital defects. These older (34 years of age and more) mothers were the ones in whom vaginal bleeding during the first trimester of pregnancy appeared to be related with the appearance of Mongolism in the baby. In this series about 30 per cent

of older mothers of Mongoloid babies gave evidence of uterine hemorrhage, whereas less than 4 per cent of the controls were recorded to have bled or stained in the first 3 months of gestation.

Aging, the mere accumulation of years, can hardly be regarded as a cause of disease, per se. Counting birthdays is an oversimplified measure of many things besides time. Age is a useful clue, however, by which to center on maternal stresses suspect of registering progressively adverse effects upon the embryo. Rh sensitization, for example, increases with the years if the passage of time is marked by successive pregnancies or transfusions. Likewise cardiovascular, renal, and other chronic diseases—tumors, diabetes, hypothyroidism, heart disease, and anemia, and intrauterine accompaniments such as hydramnios[17]—also tend to become chronic and get worse as the months and the years go by. The evolution of prediabetes into frank diabetes and the relation to congenital deformities of the infant is an illustration.

Such chronic disorders are variously systemic, gynecologic, or additive in their manifestations. For the fetus, however, a localized disease of the uterus might well have a systemic impact; and the nature of Mongoloid stigmas points to a systemic stress as the ultimate causative mechanism. The importance of cumulative maternal factors is indicated by the data elicited in this study of the mothers' histories; but the significance of these findings cannot be measured by conventional statistical tests. These stresses were acting during the first trimester of life to maim the differentiating brain, eyes, heart, and little finger.

A beginning control of this lifelong blight of the central nervous system may come sooner than proof of suspected factors—maternal heart disease or threatened abortion, for example—as the clinical and epidemiologic facts are brought together, interpreted, expanded, and given meaning. Meanwhile, suspected factors that are accentuated by maternal aging need further analysis at the bedside, in the laboratory, and in the field. They are variously endocrine, gynecologic, systemic, and combined. The problems involved are primarily biologic and gynecologic rather than statistical. Statistical studies of secular and geographical distributions are needed, however, even as they are for poliomyelitis, in order to evaluate the effectiveness of preventive measures that might seem reasonable—and may or may not be effective.

The indications for applying clinical and epidemiologic procedures in a connected fashion to the problem are as clear as the indications that led to the control of smallpox and diphtheria. The relation of Mongolism to maternal ill health deserves intensive study. The relation to age alone implies that chronic rather than acute processes may be involved; and a definite excess of chronic conditions—manifestations of heart and vascular disease and gynecologic disturbances in older mothers especially—was observed in this study of 52 pregnancies productive of Mongoloid babies compared with 52 other pregnancies selected as controls with the mothers matched for age.

It is provocative to compare the finding retrospectively determined that there is an association between Mongolism and bleeding during pregnancy

with the prospective observation of Turnbull and Walker.[19] They followed the outcome of 155 pregnancies that were complicated by bleeding (apparently successfully treated) and found that 19 per cent subsequently terminated in death of the conceptus and that the incidence of congenital deformity was about twice that expected by chance. They also found that hemoglobin and red blood cell levels in the surviving babies' cord blood at birth were higher than normal and inferred that with a history of threatened abortion the oxygen supply may have been abnormally curtailed. Such an interpretation is consistent with significantly lower birth weights, placental weights (by gestational age),[5] the laxness almost amounting to asphyxia observed by Øster, and the low oxygen saturation found in the blood of 2 Mongoloid babies at birth by Apgar and her co-workers.[18] Oxygen saturation determinations on capillary blood were reported as 15 per cent and 28 per cent, respectively.

Summary and Conclusions

The relation of Mongolism to maternal health in the first trimester of pregnancy was studied in the 52 mothers who gave birth to Mongoloid babies in the years 1935 through 1954 at the Boston Lying-in Hospital. Their health and reproductive performance were compared with those of 52 age-matched controls.

The relation of Mongolism to maternal age was again confirmed and hitherto unrecognized associations with cardiovascular and gynecologic disorders were uncovered. By separating both the test and the control series into two age groups it became apparent that the factors probably causing Mongolism in the progeny of women nearing the menopause are quite different from the factors related to disease of the baby in women 33 years old or less. It is of interest and probably significant that only one of 22 younger mothers of Mongoloid babies and only one of their controls had first trimester vaginal bleeding, whereas it was recorded in 9 of the 31 older mothers. With retroflexion of the uterus the predicament of the two groups of mothers was reversed. Retroversion was recorded on the charts of 9 of 21 (43 per cent) of the younger mothers of Mongoloid babies and on only 3 of the charts of their controls. As an isolated finding this is hardly significant. As a clue, however, it is considered important to explore further.

The evidence points to the origin of Mongolism in multiple acute and chronic maternal stresses that are nonspecific in character and additive in their impact on the conceptus during the first trimester of pregnancy. The future challenge is to plot the extent of secular changes at other hospitals and also to compare geographical differences in order to determine meaning and methods of prevention. To this end Mongolism should be made a reportable disease at hospital and state levels.

Findings to date suggest that Mongolism may be among the first of the congenital anomalies that can be significantly reduced by intentional measures

practiced during antenatal life upon the person of the mother. Older women especially should have a prepregnancy checkup for the purpose of identifying and rectifying chronic systemic and gynecologic disorders.

References

1. Ingalls, T. H.: Am. J. Dis. Child. **74**: 147, 1947.
2. Benda, C. E.: Mongolism and Cretinism, New York, 1946, Grune & Stratton.
3. Carter, C., and MacCarthy, D.: Brit. J. Social Med. **5**: 83, 1951.
4. Smith, A., and Record, R. G.: Brit. J. Prev. & Social Med. **9**: 51, 1955.
5. Smith, A., and McKeown, T.: Arch. Dis. Childhood **30**: 257, 1955.
6. Ingalls, T. H.: Am. J. Dis. Child. **73**: 279, 1947.
7. Benda, C. E.: J. A. M. A. **139**: 979, 1949.
8. Øster, J.: Mongolism, Copenhagen, 1953, Danish Sc. Press, Ltd.
9. Kurland, L. T.: Personal communication, 1956.
10. Pugh, T. H.: Unpublished data.
11. Bleyer, A.: Am. J. Dis. Child. **55**: 79, 1938.
12. Van der Scheer, W. M.: In Bonhoeffer, K.: Abhandlungen aus der Neurologie, Psychiatrie und ihren Grenzgebieten, Berlin, 1927, S. Karger, no. 44.
13. Jenkins, R. L.: Am. J. Dis. Child. **45**: 506, 1933.
14. Beidleman, B.: Am. J. Ment. Deficiency **50**: 35, 1945.
15. Thalhammer, O.: Wien. med. Wchnschr. **66**: 165, 1954.
16. Schröder, H.: Ztschr. ges. Neurol. u. Psychiat. **163**: 390, 1938.
17. Prindle, R. A., Ingalls, T. H., and Kirkwood, S. B.: New England J. Med. **252**: 555, 1955.
18. Apgar, V., Girdany, B. R., McIntosh, R., and Taylor, H. C., Jr.: Pediatrics **15**: 653, 1955.
19. Turnbull, E. P. N., and Walker, J.: J. Obst. & Gynaec. Brit. Emp. **63**: 553, 1956.
20. Versari, R.: Ricerche n. lab. di anat. norm. d. r. Univ. di Roma **10**: 25, 1903.

Gynecology

VARIATIONS IN BODY WEIGHT AND SALIVARY SODIUM IN THE MENSTRUAL CYCLE*

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ALTHOUGH premenstrual edema must have been noticed in some women by our remote forebears and was occasionally mentioned by earlier writers, credit is generally given to W. A. Thomas[12] for the first description of the condition. He published 2 case reports in 1933; these women gained up to as much as 14 pounds "at" or "during" the menstrual period and had generalized edema at the time. Okey and Stewart,[9] in the same year, reported that no significant weight changes were detected at the time of menstruation in 75 per cent of 20 college women who were weighed daily for a month. In the other 25 per cent there was a gain of 1 to 3 pounds shortly before the onset of menstruation, with a fall in weight when the period began. In the next year, Sweeney[10] described the weight changes in 42 nurses who weighed themselves daily, beginning 10 days before the next expected menstrual flow and continuing through until 10 days after menstruation. Approximately 30 per cent of the nurses gained 3 pounds or more "during or about their menstrual cycle." Some had no weight change and some lost a pound or two. Subsequently, several other writers[7] have reported that approximately 30 per cent of women have weight gains associated with menstruation. Novak and Novak,[8] in their *Textbook of Gynecology,* wrote that the 30 per cent incidence "agrees with our own experience."

Thorn, Nelson, and Thorn[14] suggested that the premenstrual weight gain represents salt and water retention, mediated by estrogenic hormones. They and Thorn and Engel[13] found that subcutaneous injection of 5 mg. of alpha-estradiol or 15 mg. of estrone, in dogs, resulted in decreased 24 hour excretions

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of sodium, chloride, phosphate, nitrogen, and water. Progesterone also reduced sodium and chloride excretion. They also did balance studies in 4 women and found that 3 of them had reduced sodium excretion during the 3 days just before menstruation. Long and Zuckerman[6] believed that the salt-retaining adrenal cortical hormones may play a part in the alleged disturbance of electrolyte balance associated with menstruation.

In view of the presumed premenstrual salt and water retention and the possible role of salt-retaining steroids in the process, it seemed interesting to follow some normal women in the manner to be described.

The concentration of sodium in saliva (as in sweat and milk) is said to reflect the activity of salt-retaining steroidal hormones.[3, 4, 5, 15] The evidence is as follows: In Addison's disease (decreased adrenal cortical activity) the salivary sodium concentration is higher than normal, while in Cushing's syndrome (increased adrenal cortical activity) the salivary sodium concentration is low. When normal (or abnormal) subjects are injected with desoxycorticosterone, cortisone, or adrenocorticotropic hormone, the salivary sodium falls sharply. Activity or anxiety (stimulation of the adrenal cortex) decreases the salivary sodium level. Frawley and Thorn[4] concluded that "the salivary Na/K ratio affords a simple means of following changes in adrenal cortical activity in terms of electrolyte regulation." The hormonal effects upon salivary potassium are less clear-cut, and either are opposite to the effects upon sodium or are insignificant. It has not been established that the sex steroids have the same effect as the adrenal cortical steroids, but it seems reasonable to suppose that any salt-retaining hormone would affect the salivary sodium concentration.

An apparent advantage of the measurement of salivary sodium concentrations is that they may reflect the physiologic activity of salt-retaining hormones. Measurements of the urinary excretion of such hormones, or of their metabolites, do not necessarily mirror activity; it is conceivable that hormone molecules excreted in the urine may have had no physiologic effect.

Material and Methods

The first series of women consisted of 16 stenographers, clerks, technicians, and interns who worked in or near our department. All were free of menstrual disorders and their ages ranged from 20 to 37 years (mean, 27); 5 were married and 3 had borne children. They were followed through 2 menstrual cycles, between October, 1953, and January, 1954. These women collected about 5 ml. of saliva as soon as they arose in the morning, after rinsing out their mouths with water. The flow of saliva was not stimulated artificially (as, for instance, by chewing paraffin). Such "stimulated" saliva has considerably higher sodium concentrations than does "unstimulated" saliva. When the women came in for the day's work, at about 9 A.M., they were weighed in their stocking feet and underclothes. One carefully adjusted beam balance was used for all weighings.

The second series of women consisted of 7 young hospital nurses, studied between February and April, 1956. Two had some premenstrual tension but

otherwise there were no menstrual disorders. The nurses kept their own daily weight and basal temperature records through 2 menstrual cycles. Salivary studies were not done in this series.

Salivary sodium and potassium analyses were done with a flame photometer, with an internal lithium standard. Centrifuged saliva was usually diluted 1:25 for sodium and 1:125 for potassium assays. Because of the viscosity of the less dilute solutions, a vaporizer with a large orifice was used in the flame photometer.

Five subjects were given a daily supplement of 5 Gm. of sodium chloride, in tablets, for the last 2 weeks of their menstrual cycles.

Results

Premenstrual Weight Changes.—The two series of women have been combined for the analyses of weight changes during the menstrual cycle. As was noted by Thomas,[11] each subject had rather marked variations in body weight throughout the cycle. Individual graphs of our daily weights did not show any definite and sustained weight gains limited to the premenstrual days. For this reason, the data have been analyzed in several other ways.

Data are available for 40 menstrual cycles, beginning with the first day of bleeding through to the onset of the next menses (with some days missing, as noted above). Table I shows a condensation of the first analysis. In the original tabulation, the day of the cycle in which the maximal weight occurred was recorded. In many instances the same maximal weight was observed on 2 or more days, in which cases it was recorded for each of the days on which it occurred. Thus, from 40 cycles, 66 maximal weights were recorded. One adjustment was made, to bring all cycles to 28 days. In cycles of more than 28 days, the first 18 days and the last 10 before the onset of the next period were recorded. In cycles of less than 28 days, the last 10 before the onset of the next period were recorded and observations were not duplicated in the tabulations for days 18, 17, etc.

TABLE I. DAYS OF THE MENSTRUAL CYCLE ON WHICH MAXIMAL BODY WEIGHTS WERE OBSERVED

	DAYS OF CYCLE					EIGHTH TO FIFTH DAYS PRECEDING ONSET OF MENSTRUATION	FOURTH TO FIRST DAY PRECEDING ONSET OF MENSTRUATION
	1 TO 4	5 TO 8	9 TO 12	13 TO 16	17 TO 20		
No. of maximal weights	6	4	10	11	13	10	12
Percentage of maximal weights	9.1	6.1	15.1	16.7	19.7	15.1	18.2

In Table I, it appears that exactly one third of the maximal weights were observed in the 8 days preceding the next menstrual flow. This is in accord with the incidence of premenstrual weight gain recorded by others. However, as will be shown in the comment, this probably arises by chance.

The second analysis, shown in Table II, does not support the idea that there is a significant premenstrual weight gain. Data are available for the weight changes between the fifth and first days preceding 33 menstrual periods. In 13 there was a gain of weight, in 14 a loss, and in 6 no change. Only in 3 instances did the weight gain exceed 1 pound in this 5 day period; the maximal gain at this time was 2 pounds. In 51 cycles the weight changes from the first to the third day of menstruation have been tabulated. As Table

II shows, weight gain was observed in 18, weight loss in 17, and no change in 16. Only in 2 instances did the weight change exceed 1 pound. The data for the next 5 days (days 4 to 8) show that in 47 cycles weight gain occurred in 19, weight loss in 22, and no change in 6. In 13 cycles the weight change was greater than 1 pound over these 5 days, ranging from plus 4 to minus 5 pounds. No subject showing a premenstrual weight gain in one cycle duplicated this pattern in her other cycle that was studied.

TABLE II. WEIGHT CHANGES IN RELATION TO THE MENSTRUAL CYCLE

	WEIGHT GAIN			WEIGHT LOSS			
DAYS OF THE CYCLE	NO.	MORE THAN 1 POUND	MAXIMAL GAIN (POUNDS)	NO.	MORE THAN 1 POUND	MAXIMAL LOSS (POUNDS)	NO CHANGE
Last 5 premenstrual days	13	3	2	14	5	2.25	6
First 3 days of menstruation	18	1	4	17	2	3	16
Next 5 days (days 4 to 8)	19	6	4	22	7	5	6

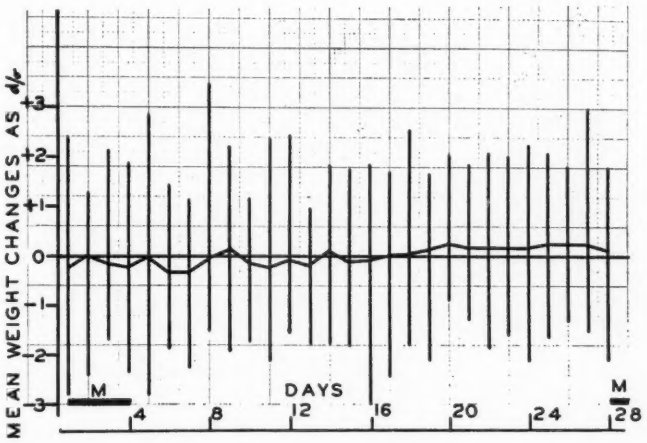

Fig. 1.—Weight changes in the menstrual cycle. The mean body weight and its standard deviation were calculated for each subject. Each day's deviation of the weight from the mean was then divided by the standard deviation; these quotients (d/σ) were then averaged for each day. The solid, wavy line shows these averages, while the vertical bars show the range of the quotients. One standard deviation is about 1.1 pounds (0.5 kilogram).

The results of the third analysis are shown in Fig. 1, which averages all of the observations. Inasmuch as the body weights of the subjects under study varied from 92 to 165 pounds, and the women were not weighed every day, one cannot simply average the body weights for each day of the cycle. The cycles were adjusted to 28 days, in the manner described. In order to average all of the observations, the mean weight and its standard deviation were calculated for each subject. For each case, the deviation from the mean weight on each observation was divided by the standard deviation for that subject, as was done by Danforth, Boyer, and Graff.[1] Thus, if an individual's standard deviation was 1 pound and an observed weight was 2 pounds above or below the individual's average, the quotient, d/σ, would be ±2. These numbers can be averaged as they were for the construction of Fig. 1. In addition to the average, the extreme plus and minus variations are shown for each day of the cycle. Although the average curve does rise above zero in the last 10

days before menstruation, the average weight is no more than one fourth of a standard deviation above the mean. Again, it appears that there is no significant premenstrual weight gain.

Salt Supplement.—When it became evident that these subjects were not gaining weight significantly in the premenstrual period, an effort was made to induce such gains by feeding a salt supplement. Five of the women took salt tablets (5 Gm. of sodium chloride) daily during the latter half of their menstrual cycles; this, of course, was in addition to their ordinary salt intake. All had transitory weight gains in the first day or two, but none showed a significant premenstrual gain in weight. Their weight changes, from the fifth to the first premenstrual days were plus 1, minus 1, minus 1, minus 1½, and minus 2½ pounds.

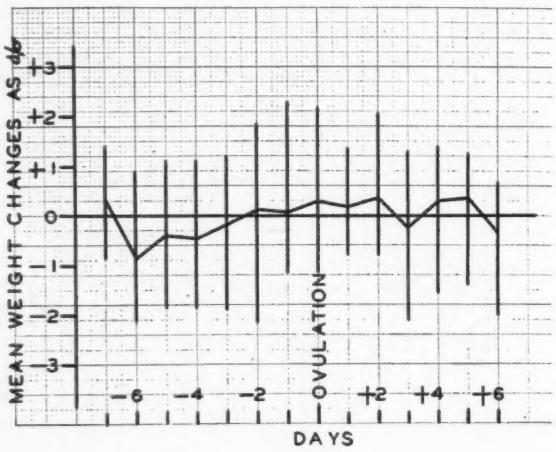

Fig. 2.—Weight changes at about the time of ovulation, in 15 cycles in which the date of ovulation was deduced from the basal body temperature curve. The data were derived and plotted as in Fig. 1.

Weight Changes at the Time of Ovulation.—The data shown in Tables I and II and in Fig. 1 gave no suggestion that weight is gained at the time of ovulation. However, the ovulation times are not known in many of the cycles. For this reason a separate analysis was made of the data for the 15 cycles in the 7 nurses who had made daily recordings of their basal body temperatures.

The maximal weight recorded in any of 3 days beginning with the day of ovulation was greater than the average weight over the 3 days preceding ovulation in 9 cycles, less in 5, and the same in 1. However, all of the weight gains were well within the range of fluctuation observed at any time in the cycle; only 3 of the gains exceeded 1 pound. The range of weight changes was from minus 1.25 to plus 2.0 pounds. The average gain in all 15 cycles was plus 0.4 pounds.

Fig. 2 presents an analysis similar to that in Fig. 1; the data for the daily weight changes are averaged for the 15 cycles in which ovulation was dated by the basal temperature records. The mean weight and its standard deviation were calculated for each subject. The variation of each day's weight from the subject's mean weight was then divided by the standard deviation and the quotients (d/σ) were averaged for each day. While the mean quotients do increase at about the same time of ovulation, the greatest average increase is only one third of a standard deviation. In summary, the subjects studied did not show significant weight changes at the time of ovulation.

Salivary Sodium and Potassium.—Although the data were analyzed in several ways, they could not be tortured into showing any marked cyclic variation. Table III shows the means and their standard deviations for both salivary sodium and potassium concentrations at various periods in the menstrual cycle. No significant changes are evident in the table.

In order to average all of the observations, the same method of analysis that was used for Figs. 1 and 2 was applied (calculation of d/σ and averaging these values for each day). As Fig. 3 shows, the salivary sodium did not change significantly during the menstrual cycle. However, in 10 of the 11 immediately premenstrual days, d/σ is on the minus side but by no more than one third of a standard deviation. The same subjects, in the same 11 premenstrual days, did show weights slightly above average (Fig. 1), that is, d/σ on the plus side but by no more than one fourth of a standard deviation. Thus, the weight change and the salivary sodium concentration appear to bear an inverse relation, which is also present in the first half of the cycle. This is

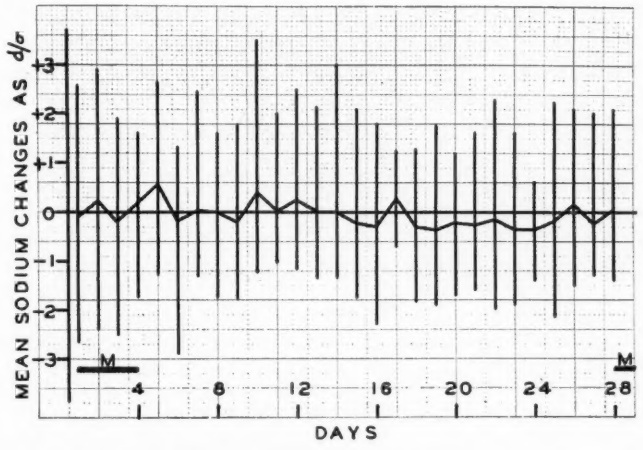

Fig. 3.—Variations in salivary sodium throughout the menstrual cycle. The data were derived and plotted as in Fig. 1.

what one might expect if the weight changes depended upon the activity of salt-retaining hormones. The changes in both weight and salivary sodium are so slight as to be insignificant, however.

TABLE III. SALIVARY SODIUM AND POTASSIUM CONCENTRATIONS IN THE MENSTRUAL CYCLE

	DAYS 1 TO 3		DAYS 4 TO 8		3 DAYS, MIDCYCLE		SIXTH TO FOURTH DAYS PRECEDING ONSET OF MENSTRUATION		THIRD TO FIRST DAYS PRECEDING ONSET OF MENSTRUATION	
	MEAN	SIGMA	MEAN	SIGMA	MEAN	SIGMA	MEAN	SIGMA	MEAN	SIGMA
Sodium	19.4	7.8	18.2	7.2	18.7	5.5	17.4	5.8	18.1	6.6
Potassium	23.3	4.8	22.3	4.2	23.1	4.0	23.8	4.3	23.2	4.1

The salivary potassium and Na/K ratios similarly did not show any significant cyclic variation.

Comment

While it seems to be almost generally agreed that about 30 per cent of women do have a weight gain near the time of the menstrual period, with a subsequent weight loss, there is a disagreement as to the exact time relations.

Okey and Stewart[9] wrote that the weight gain occurred shortly before the period, with a sharp fall when menstruation began. Thomas[11] found the peak in weight just before, coincident with, or just following the onset of bleeding; the weight loss occurred later, with the minimal weight reached between the seventh and twelfth days. Thorn, Nelson, and Thorn[14] found a weight gain premenstrually in 48 per cent of their cases, with weight loss during menses in 44 per cent. Postmenstrually, only 4 per cent of their patients lost weight.

The data of Thomas are of particular interest, for she published graphs of the daily weights of each of her 14 subjects (women medical students). There were marked variations throughout the cycle, with 7 or more peaks of weight during the month. Six of the 10 "most regular subjects" showed their maximal weights at about the time of menstruation (before, during, or after the onset); the other 4 reached their maximal weights at some other time. By subtracting the minimal weight at any time in the cycle from the greatest weight found near menstruation, Thomas found "premenstrual" weight gains ranging from 2 to 6⅜ pounds (mean 3.65 pounds). Obviously, this calculation would necessarily show premenstrual weight gain in many women.

Thorn, Nelson, and Thorn found the premenstrual weight gain in the 7 to 10 days before menstruation. Thomas, who found the gain just before, during, or just after menstruation, covered a similar span of time. Suppose that weight changes bear no relation whatsoever to menstruation and that the weight fluctuates in a purely random manner so that the maximal weight might have an equal probability of occurring in any day of the 4 week period. What would be the probability of finding the maximal weight in any given 7 to 10 day period? It would be close to 30 per cent, which is the incidence accepted for premenstrual weight gain.

TABLE IV. OBSERVED DISTRIBUTION OF MAXIMAL WEIGHTS IN THE MENSTRUAL CYCLE COMPARED TO DISTRIBUTION EXPECTED ON THE BASIS OF CHANCE

	DAYS OF CYCLE			EIGHTH TO FIRST DAY PRECEDING ONSET OF MENSTRUATION	TOTAL
	1 TO 8	9 TO 16	17 TO 20		
No. of maximal weights observed	10	21	13	22	66
No. of maximal weights expected by chance	19	19	9	19	66
Chi square	3.6	0.14	0.86	0.32	–

Table IV is based upon the same data as Table I, and shows the numbers of observed maximal weights in relation to days of the menstrual cycle. The second line shows the numbers of maximal weights to be expected in the same time periods, if chance alone determined their distribution. The third line shows that the distribution of maximal weights observed does not differ significantly from chance distribution.

It appears that previous workers are correct in finding that some 30 per cent of women attain their maximal weights at or near the menstrual period. The null hypothesis, applied in the last paragraph, suggests that this is a matter of chance, for in any comparable time span in the cycle, similar peaks in weight might be found with essentially the same frequency (as they were in the present study).

Undoubtedly, some women do have premenstrual edema associated with definite weight gain. This, together with the proved salt-retaining effect of the sex steroids[2] and their physiologic increase in the premenstrual periods, points logically to a general phenomenon of premenstrual weight gain. When

such weight gains were found (in some 30 per cent of women), everything seemed to be tied up in a neat package and premenstrual weight gain has come to be accepted as physiologic. However, two considerations seem to have been overlooked: (a) the possibility of chance variations as discussed above and (b) the fact that the majority (about 70 per cent) of women do not have premenstrual weight gains.

Finally, let us look again at Fig. 1. While it does not show any significant weight change at any time in the cycle and does not show any sustained upward trends in weight, it does show that during the 10 days preceding menstruation the curve is consistently above the zero line. If the times at which maximal weights were observed were perfectly random, then the chances would be even on any given day for d/σ to fall above or below the zero line. The chances of its falling above the line for 10 consecutive days would be $(\frac{1}{2})^{10}$, or 1 in 1,024. Moreover, the average weights are usually below the zero line in the first half of the cycle. Thus it appears that the average body weight is slightly increased during the last 10 days before menstruation. However, the curve does not show a progressive weight gain; what it does show is a slight increase on the tenth and ninth days before menstruation, with a fair plateau thereafter. The highest point on the curve, on the ninth day before menstruation, is only one fourth of a standard deviation from the mean. This amounts to only a quarter of a pound.

Summary and Conclusions

Twenty-three normal women were followed through at least two menstrual cycles. Basal body temperature records were kept by the 7 nurses in the series and salivary sodium and potassium measurements were made in the other 16.

In one third of the women, the maximal weight was observed to occur in the last 8 days preceding menstruation. This is in accord with the reported incidence of premenstrual weight gain.

Closer analysis of the data did not substantiate the concept of premenstrual weight gain as a physiologic phenomenon. When such weight gains did occur, they were slight and no women who had such premenstrual weight gain in one cycle duplicated it in the other cycle studied.

The time spans in which premenstrual weight gains have been reported to occur are such that a purely random distribution of maximal weights, by days of the cycle, would give the same incidence of premenstrual weight gain as has been reported by others.

On the average, there is a sustained increase in body weight over the last 10 days before menstruation. This is not a progressive gain, but occurs on the tenth and ninth days before menstruation; after this gain, a fair plateau is maintained. During this 10 day period, the body weight is only about a quarter of a pound above the average for the whole cycle.

The salivary sodium concentration, which may reflect the physiologic activity of salt-retaining hormones, does not show any significant variation during the menstrual cycle. In the last 10 days before menstruation, when the average body weight is slightly increased, the average salivary sodium concentration is slightly decreased.

It appears probable that premenstrual weight gain is not a physiologic phenomenon. The reported incidence could arise by chance alone.

References

1. Danforth, D. N., Boyer, P. K., and Graff, S.: Endocrinology **39**: 188, 1946.
2. Dignam, W. S., Voskian, J., and Assali, N. S.: J. Clin. Endocrinol. **16**: 1032, 1956.
3. Dreizen, S., Niedermeier, W., Reed, I. A., and Spies, T. D.: J. D. Res. **31**: 271, 1952.
4. Frawley, T. F., and Thorn, G. W.: In Note, J. R., editor: Proc. Second Clinical ACTH Conference, Philadelphia, 1951, Blakiston Company, vol. 1, p. 115.
5. Grad, B.: J. Clin. Endocrinol. **12**: 708, 1952.
6. Long, C. N. H., and Zuckerman, S.: Nature **139**: 1106, 1937.
7. Morton, J. H., Additon, H., Addison, R. G., Hunt, L., and Sullivan, J. J.: Am. J. Obst. & Gynec. **65**: 1182, 1953.
8. Novak, E., and Novak, E. R.: Textbook of Gynecology, ed. 5, Baltimore, 1956, Williams & Wilkins Company, p. 736.
9. Okey, R., and Stewart, D.: J. Biol. Chem. **99**: 717, 1933.
10. Sweeney, J. S.: J. A. M. A. **103**: 234, 1934.
11. Thomas, C. B.: Ann. Int. Med. **39**: 289, 1953.
12. Thomas, W. A.: J. A. M. A. **101**: 1126, 1933.
13. Thorn, G. W., and Engel, L. L.: J. Exper. Med. **68**: 299, 1938.
14. Thorn, G. W., Nelson, K. R., and Thorn, D. W.: Endocrinology **22**: 155, 1938.
15. White, A. G., Gordon, H., and Leiter, L.: J. Clin. Invest. **29**: 1445, 1950.

TEEN-AGE DYSMENORRHEA*

A Statistical Evaluation of the Role of Suggestion in Treatment

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DYSMENORRHEA is a symptom complex characterized mainly by lower abdominal pain at the time of the menses. It is a major cause of disability in high schools, in colleges, and in industry. There are many theories concerning the mechanism by which the pain is produced and doubtless there is more than a single factor involved; yet psychological factors have frequently been mentioned as important in therapy. In this study, we have tried to evaluate statistically some of the aspects of the role of suggestion in the management of dysmenorrhea.

Plan of Study

Our approach in determining the effect of suggestion in dysmenorrhea was carried out with the full cooperation of the Divisions of Special Education, and Physical and Health Education of The Board of Public Education of Philadelphia. Two replicate studies were done in two pairs of secondary schools. The four schools are listed as Ax and Bx (experimental schools) and Ac and Bc (control schools). The first study with schools Ax and Ac was carried out with 1,049 girls from Jan. 1, 1953, to June 1, 1953, the second with 1,657 girls from Nov. 1, 1953, to Nov. 1, 1954. A total of 2,706 girls was included in the full study.

The various schools, experimental and control, did show some differences in the number of teachers involved and in percentage of white and non-white students. Ac has 8 physical education teachers; and 60 per cent of the student population is non-white; Bc is a vocational technical school with 3 teachers and about 34 per cent non-white students; Ax has 7 teachers and 17 per cent non-white students; Bx has 11 teachers and no non-white students.

All girls in both studies received the same routine body conditioning exercises as part of their physical education instruction. At the beginning and end of each of the time periods previously mentioned a general health questionnaire was distributed to each student asking about the current presence or absence of dysmenorrhea among other medical conditions. Throughout the school year the teachers of the experimental schools frequently stated that the exercises would help treat dysmenorrhea. No particular mention of any possible effect of the exercises on dysmenorrhea was made at the control schools.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Oct. 4, 1956.

Results

A summary of our results is presented in Table I and Fig. 1. It is to be noted that the incidence of dysmenorrhea was not the same at every school at the start of the experiment. The two control schools (Ac, Bc) and one experimental school (Ax) were comparable with a combined incidence of 42.9 per cent; the incidence of dysmenorrhea at one experimental school (Bx) was significantly lower at 28.5 per cent. A possible partial explanation for this is the absence of non-white in this school, dysmenorrhea being more common in the non-white.[1] None of the schools showed any significant change in the incidence of dysmenorrhea from the beginning to the end of the experiment.

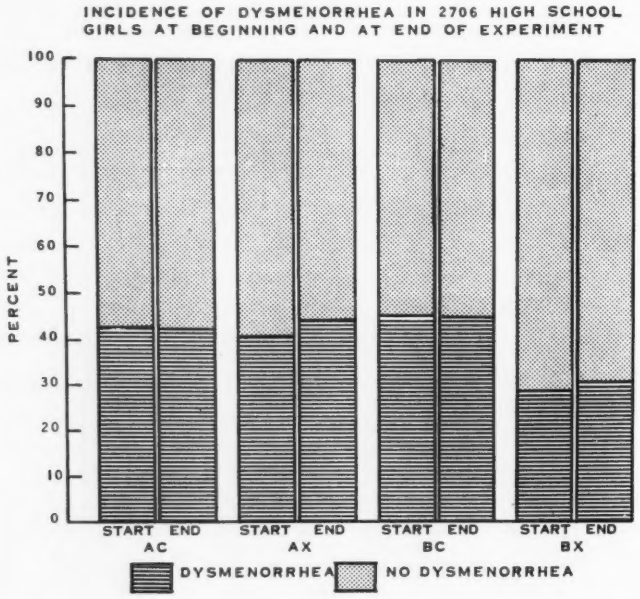

Fig. 1.

TABLE I. RESULTS OF STUDY OF THE ROLE OF SUGGESTION IN THE TREATMENT OF DYSMENORRHEA

	TOTAL NUMBER OF GIRLS	INCIDENCE OF DYSMENORRHEA (%)		% WITH DYSMENORRHEA AT START WHO HAD NO DYSMENORRHEA AT END	% WITHOUT DYSMENORRHEA AT START WHO HAD DYSMENORRHEA AT END
		AT START	AT END		
Control Schools.—					
Ac	624	42.5	42.3	20.4	14.8
Bc	553	45.0	44.7	24.1	19.1
Experimental Schools.—					
Ax	425	40.7	44.2	21.4	20.6
Bx	1,104	28.5	30.2	25.4	12.4

Of those free of dysmenorrhea at the start of the study, 12.4 to 20.6 per cent suffered from dysmenorrhea at the end of experiment (Fig. 2). School-to-school differences cannot be explained on the basis of psychological suggestion since: (a) no mention was made to the girls of any efficacy of exercise

in *preventing* dysmenorrhea, and (b) there was no consistency in the school-to-school differences as evidenced by the fact that the two experimental schools had the highest and the lowest percentages of all four groups.

There was no significant school-to-school difference in proportion of girls "cured" of their dysmenorrhea (Fig. 3). Hence, there is no evidence that dysmenorrhea can be cured by the type of psychological suggestion employed in this

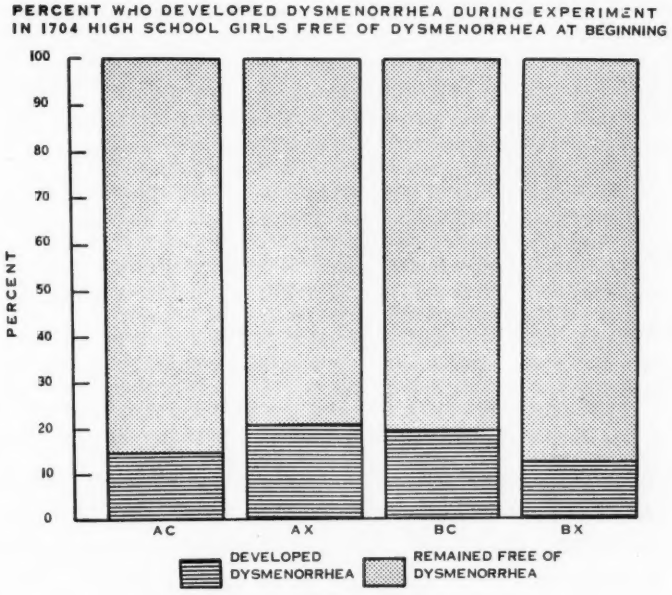

Fig. 2.

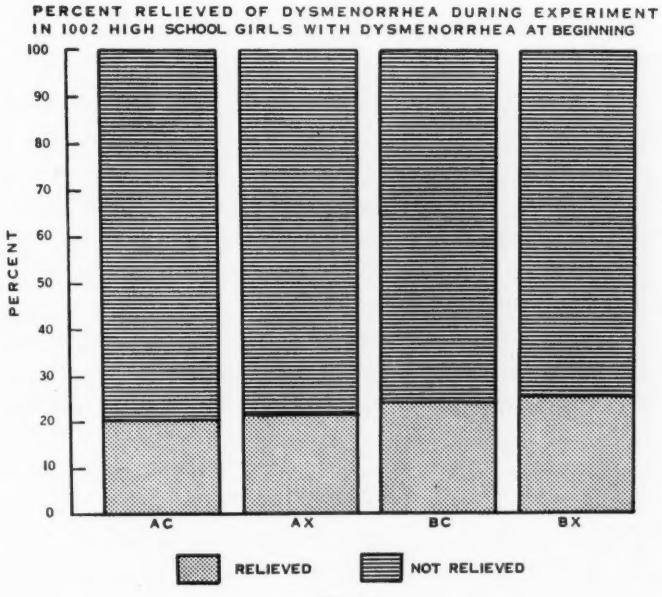

Fig. 3.

study. Altogether, 23.1 per cent were relieved of dysmenorrhea; this may be taken as an estimate of the proportion of cases which resolve themselves "spontaneously" over an interval of six months to a year.

Comment

There are several aspects of our particular approach to the dysmenorrhea problem that deserve discussion. In the first place, it would have been desirable to collect the data separately for white and non-white students. This was not feasible. Then, too, although all teachers were given the same orientation, there is no guarantee that they were equally objective and cooperative. Some may have stressed the beneficial aspects of exercise while others may have been less energetic in their praises. So far as we can determine, the general attitude of the teachers in the various schools was favorable to the project under consideration. While all students filled out identical questionnaires there may have been some differences in interpretation on the part of either the teacher or student as to the severity of discomfort sufficient to be classified as dysmenorrhea. Perhaps in future studies it would be wise to have each instructor responsible for both a control and an experimental group to control teacher-to-teacher variation as well as school-to-school variation.

It was not our intent in this study to evaluate the effectiveness of exercise in the treatment of dysmenorrhea; in fact, from our data no conclusions whatsoever can be made as to the merit of exercise in itself. It has been reported[2] that women who exercise have a lower incidence of dysmenorrhea and on the other hand[3] that those who do not participate in sports have no more interference with normal routine at the time of menses than those who do. Special exercises have been proposed[4, 5, 6] and seem to have value.

Most writers on the management of dysmenorrhea stress the significance of the psychic factor. Case reports are often cited. Wittkower and Wilson[7] found that dysmenorrheic patients were less well adjusted as children than were controls. Using a word-association test, Boyd and Valentine[8] report that patients with dysmenorrhea tend to demonstrate more anxiety about bodily functions than those without dysmenorrhea. Haman[9] found a lowered threshold of pain in those with dysmenorrhea but which of the two—low threshold or dysmenorrhea—is cause or effect can naturally not be specifically determined. While there are undoubtedly psychoneurotic dysmenorrheic patients, by no means is there general agreement on the psychogenic basis for dysmenorrhea. Schuck,[10] after an analysis of the health records of students with and without dysmenorrhea, found no difference in psychoneurotic manifestations. Bickers[11] stated that "most disease states are classified as psychic until their true etiology is learned."

Summary

1. A total of 2,706 girls of four secondary schools in two separate experiments were questioned about dysmenorrhea before and after a period of routine body-conditioning exercises. Students of the experimental schools were repeatedly told that the exercises would cure dysmenorrhea; students of the control schools were told nothing about any possible effect of the exercises on dysmenorrhea.

2. None of the schools showed any significant change in the incidence of dysmenorrhea from the beginning to the end of the experiment.

3. Of those free of dysmenorrhea at the beginning of the experiment, 12.4 to 20.6 per cent suffered from dysmenorrhea at the conclusion.

4. There was no significant difference in "cure" rate between control and experimental schools. Altogether, 23.1 per cent of those with dysmenorrhea were relieved of dysmenorrhea. This figure may be taken as an estimate of the proportion of teen-age cases which resolve spontaneously during an interval of six months to a year.

Sincere appreciation is expressed to Mr. Walter Biddle Saul, former President of The Philadelphia Board of Public Education, Mr. Grover W. Mueller, Director of Physical Education, Dr. Ruth H. Weaver, Medical Director, Miss Josephine Christaldi, Miss Dorothy McQueen, and the many teachers and nurses who made possible this study. We also give credit to Mr. Joseph Bruno and Miss Florence Schaal, Physiotherapists of St. Luke's and Children's Medical Center, Philadelphia.

References

1. Golub, L. J.: Unpublished data.
2. Menstruation in Schoolgirls; Survey Based on Replies to a Questionnaire, Lancet **2**: 57, 1930.
3. Drillien, C. M.: J. Obst. & Gynaec. Brit. Emp. **53**: 228, 1946.
4. Billig, H. E., Jr.: Arch. Surg. **46**: 611, 1943.
5. Dick, A. E., Billig, H. E., Jr., and Macey, H. N.: Indust. Med. **12**: 588, 1943.
6. Golub, L. J., and Brown, J. O.: In preparation.
7. Wittkower, E., and Wilson, A. T. M.: Brit. M. J. **2**: 586, 1940.
8. Boyd, P. S., and Valentine, M.: Brit. J. M. Psychol. **26**: 58, 1953.
9. Haman, J. O.: Am. J. Obst. & Gynec. **47**: 686, 1944.
10. Schuck, F.: Am. J. Obst. & Gynec. **62**: 559, 1951.
11. Bickers, W.: South. M. J. **36**: 192, 1943.

Discussion

DR. MARY DE WITT PETTIT.—Dr. Golub and his associates have made an effort to evaluate the benefit of group psychotherapy in the management of dysmenorrhea in school girls. Their results and conclusions will reinforce the opinion of many of us that while there are undoubtedly psychoneurotic dysmenorrheic patients, there are also many with dysmenorrhea who do not show other objective evidence of psychoneurosis.

Most of us feel that there is a lowered threshold to pain in the average patient with severe dysmenorrhea. However, there may be, for instance, a somatic cause for fluid retention in the premenstrual phase due to hormone imbalance. Some patients actually gain 4 to 5 pounds before each period. One could postulate that the cerebral cortex may have its share of edema and ischemia in the presence of retained salt and water. This in turn may lower the pain threshold and result in patient recognition of pain in the area of pelvic congestion. Which then is the cause and which is the effect?

In such a study as Dr. Golub's, individual contact with patients is impossible. The spontaneous cessation of symptoms in one large group coincident with the onset of symptoms in another large group kept Dr. Golub's percentages very uniform. This indicates certainly that the mass psychological approach will not improve matters in this situation. That is in accord with the experience of many, that individual examination and individual confidence of the patient in her physician will play a large part in recovery. The patient's mother must also be dealt with and reassured in many teen-age situations. This involves superficial psychotherapy and above all the use of common sense. It is of the greatest importance to eliminate the organic pathological lesion such as ovarian cyst, early

endometriosis, a pelvic appendix, endocrine imbalance, and the various inflammatory conditions. Each one of the methods described for treatment will work in some percentage of cases. The trick is to individualize the treatment for the patient and to deal with her very real apprehension when her difficulty has been severe and prolonged.

DR. GOLUB (Closing).—Some years ago, in common with many other gynecologists and obstetricians, I felt that dysmenorrhea was largely psychogenic in origin. In 1952 I suggested to the members of the Special Education Committee of the Board of Education that we conduct a study to ascertain what part the "psyche" played in dysmenorrhea. I fully expected to have my preconceived notions verified.

When the results of this study were examined I was very much surprised at the absence of any evidence that dysmenorrhea could be treated by "mass psychology" and I suggested that the study be repeated in two other schools for a longer period of time, and that the teachers emphasize more strongly statements that general exercises do relieve dysmenorrhea. The results of this second trial, as you know, were similar to those of the first experiment.

Following this I analyzed the reasons for my own attitude toward dysmenorrhea: (1) The voluminous literature and editorial comments favoring the psychosomatic aspect and supported by a few case reports. (2) One study on the threshold of pain frequently mentioned. (3) The fact that patients who present themselves with dysmenorrhea are frequently nervous and upset.

A word or two about the last statement. If a person has frequent attacks of pain of gall bladder disease or of the teeth, he will become nervous and have a low threshold of pain. Admittedly, the "psyche" plays a part in dysmenorrhea as an overlay and psychoneurotic women also have dysmenorrhea. Occasionally a presacral resection has been performed for dysmenorrhea in a psychoneurotic patient, who, however, was not relieved until psychoanalysis was utilized. However, I am personally convinced that the great majority of dysmenorrheic patients are not psychoneurotic.

DISSEMINATED GRANULOMA INGUINALE AND ITS RELATIONSHIP TO GRANULOMA OF THE CERVIX AND PREGNANCY

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GRANULOMA inguinale, as the name implies, is a chronic granulomatous disease of specific etiology involving primarily skin, subcutaneous tissues, and mucous membranes of the genitals. It is usually considered a venereal disease although its transmission by coitus has not been proved. Common synonyms in the current medical literature are granuloma venereum and donovaniasis. Older terms which have been applied to this disease in the past are granuloma pudenda tropicum, granuloma inguinale tropicum, granuloma contagiosa, chronic venereal sores, and sclerosing granuloma.[11, 21] Once considered a tropical disease, in recent years it has been reported from various other parts of the world. In this country the disease occurs almost exclusively in the Negro race and is endemic in the South. Formerly, it was thought that spread occurred only by direct extension or by autoinoculation. The most recent concept, however, is that, under certain conditions, spread may also occur by either the lymphatic or the hematogenous routes, or both.

Etiology and Diagnosis

Most authors attribute the first recognizable clinical descriptions of granuloma inguinale to McLeod,[17] in India, over 60 years ago. It was not, however, until 1904, with the discovery by Donovan[7] of the constantly occurring intracytoplasmic inclusion bodies, that the infection became well defined. Since Donovan's discovery, the finding of these bodies in tissue has been regarded as diagnostic of the disease. Curiously enough, the original source of Donovan's material was a buccal lesion and not the usual genital sore.[8] Donovan and some subsequent investigators believed that the bodies were protozoa, but others described them as virus inclusion bodies or gram-negative bacilli, thought to be related to the Friedländer group. In 1925, Thierfelder[27] described a capsulated bacillus isolated from open lesions and from the blood of patients with so-called "miliary granuloma" as identical with Donovan's parasite. He named the bacillus *Microbacterium capsulatum granuloma.*

The true nature of the Donovan body was determined in 1943, when Anderson[1] and others[2] successfully cultured the bacillus in the yolk sac of the developing chick embryo. Prior to that time at least two investigators,[5, 6]

using an uncontaminated source of material, had inoculated eggs and failed to grow the bacillus because they inoculated the chorioallantoic membrane rather than the yolk sac.[5] Anderson believed, and it has since been shown fairly conclusively,[2, 26] that the "Donovan body" was an unusual bacillus which requires eggs or embryonic yolk medium for primary isolation. She named the bacillus *Donovania granulomatis.* As yet the disease has not been reproduced from pure culture.

Diagnosis of granuloma inguinale is usually made by the demonstration of *Donovania granulomatis* in the so-called "fresh tissue smear." This is best accomplished by biopsy or by scraping the lesion, macerating the tissue on glass slides, and staining with Wilson's, Wright's or Giemsa's stain. Although characteristic pathologic changes have been described, most authorities believe that an exact diagnosis can be made only when Donovan bodies are present.

The differential diagnosis must separate this entity from lymphopathia venereum, syphilis, chancroidal infection, condyloma acuminatum, carcinoma, and other granulomatous and ulcerative diseases which involve the genitals.

Extragenital Granuloma Inguinale

Extragenital lesions of granuloma inguinale are not rare and were described in the very earliest reports of the disease. In 1954, Rajam, Rangiah, and Anguli,[24] in a report from the University of Madras, stated that in the observation of over 2,000 patients with the diagnosis of granuloma inguinale, the incidence of extragenital lesions was approximately 6 per cent. This is essentially the same incidence reported by Greenblatt, Torpin, and Pund[12] in 1938. Although primary extragenital lesions have been reported, the majority usually occurs secondary to genital granuloma and is believed to be due to autoinoculation.

Extragenital sites most commonly involved are skin, subcutaneous tissues, and mucous membranes around the oropharynx, eye, and scalp. In the medical literature there are a few reports of what appears to be extragenital granuloma with involvement of bone by direct extension.

Cervical Granuloma Inguinale

It has been shown by a number of investigators that primary and secondary involvement of the cervix uteri is more common than is generally believed. Although it was suspected earlier, the first 2 proved cases were reported by Pund and Greenblatt[22] in 1937. Three years later, Arnell and Potekin[3] reported 38 cases of primary or secondary cervical granuloma inguinale seen in a 10 year period at Charity Hospital in New Orleans. At that time they were able to find only 14 previously reported cases. These authors pointed out that in 1928 Gardner[9] was the first to suggest that granulomatous lesions of the cervix which had been described by previous investigators might have been granuloma inguinale Although they believed that some of their patients had parauterine involvement, this involvement was not proved.

In 1944 Pund and McInnes[23] reported 6 fatal cases of granuloma inguinale. They stated that 3 of the 6 deaths occurred in women who had involvement of the internal pelvic viscera. The onset of symptoms in all the women dated from pregnancy. None of the 6 patients showed evidence of hematogenous spread, but Donovan bodies were demonstrated in the regional

lymph nodes. They concluded that extension occurred not only by direct continuity but also by the lymphatics, and that hematogenous spread did not occur. At that time they had 24 patients with cervical granuloma, and felt that these lesions were a serious complication of pregnancy because of the possibility of extension following delivery or abortion.

Hematodissemination of Granuloma Inguinale

In reviewing various medical reports an effort was made to identify those patients with true hematogenously disseminated granuloma inguinale, as evidenced by the occurrence of remote metastatic lesions under intact skin, and to differentiate them from other patients with (1) extragenital granuloma, primary or secondary, (2) extragenital granuloma with spread and involvement of deep tissues or bone by direct extension, (3) pelvic granuloma with extension from the cervix either directly or by lymphatics, and (4) widely dispersed lesions due to direct extension, autoinoculation, or lymphatic spread. This was a difficult task because often inadequate studies had been made and insufficient data were documented. For example, it was found that some of the reported patients with so-called "miliary granuloma" and bone involvement had what appeared to be, more likely, extragenital granuloma with bone involvement by direct extension. This seemed probable because of the lack of systemic and constitutional changes so characteristic of hematogenously disseminated granuloma.

Prior to the use of antibiotic therapy, deaths were reported which were related either directly or indirectly to widespread secondarily infected genital lesions without evidence of a generalized systemic toxic reaction. In an excellent survey of the early literature, Mayer and da Rocha Lima[15] quoted Hoffman, Kuhn, and Vogel, who had reported widespread granulomatous lesions, but the exact details of these cases were lacking, and, therefore, to draw conclusions was difficult. Becker[4] also quoted one similar case.

In 1944, Lyford, Scott, and Johnson[14] reported 3 cases of polyarticular arthritis and osteomyelitis due to *Donovania granulomatis*. In one of these patients there was systemic dissemination with widespread joint involvement, ulceration of many joints, and bone destruction. Hematogenous spread followed the removal of a large vulvar lesion in one patient. In a second patient x-ray changes were found in two vertebrae and a hip joint. These lesions communicated with a sinus tract from which Donovan bodies were recovered. The third patient had what was apparently a primary extragenital lesion of the finger which had spread by direct extension to the bones of the hand. All three of the patients were Negro females. No mention was made of pregnancy or parity. Only one of these patients was thought to have disseminated granuloma and this case represents one of the first well-documented reports of miliary-type granuloma inguinale.

The same year Paggi and Hull[19] reported a case with metastatic lesions of the left clavicle, of the right scapula, and of several ribs. The initial lesion involved the cervix and spread to the vulva. Ulceration of the left groin occurred and was believed to be the result of lymphatic drainage from the vulvar lesion. Constitutional symptoms were quite severe. Improvement of the lesions and disappearance of the general symptoms followed treatment with Diramin, a trivalent antimony compound.

Palik and Schenken[20] then reported the case of a 21-year-old Negro woman with primary granuloma of the cervix with metastatic lesions in the clavicle, rib, and scapula. The patient's parity was not stated and there was no reference to abortion or pregnancy. Smears from all the lesions were positive for Donovan bodies.

Two years later, Rhinehart and Bauer[25] reported a fatal case of disseminated granuloma of the bones. The metastases were secondary to a lesion of the cervix uteri and of the vaginal vault. Aspiration of the bone lesions revealed Donovan bodies. The autopsy confirmed the diagnosis of granuloma inguinale associated with glandular tuberculosis.

Packer, Turner, and Dulaney,[18] in 1948, reported initial involvement of the vagina, cervix, and bladder in a 19-year-old Negro girl. Subsequently the patient developed bone metastases with overlying abscesses in distant parts of the body. Dissemination and systemic manifestations were preceded by abortion. These authors emphasized the hazard, which had been expressed previously by others, of the danger of abortion or term delivery in patients with lesions of the cervix. Bacilli which morphologically resembled Donovan bodies were cultured from the patient's blood in a tryptose-peptone egg-yolk medium. Donovan bodies were also demonstrated in tissue smears from the lesions of the cervix uteri, left hand, and right knee. The patient was treated with injections of antimony potassium tartrate and showed a dramatic response. The ultimate result of treatment was not stated.

In 1950, Lipp and Bibby[13] reported involvement of the external genitals, vagina, and tibia in a 20-year-old Negro woman. Speculum examination was not done because of extensive vaginal involvement but it is unlikely that the cervix was not involved. No mention was made of pregnancy or parity.

In 1954, Rajam, Rangiah, and Anguli[24] reported a case of initial involvement of the cervix uteri which was followed by extension to the bladder, with formation of a vesicovaginal fistula and with metastases to the bones and liver. It was their opinion that dissemination followed an abortion 5 months earlier.

Case Report

Our patient was a 21-year-old single Negro woman, gravida iii, para ii, who was referred to the hospital on Jan. 24, 1955. She complained of increased vaginal discharge, migrating joint pains, swelling of the joints, weight loss, and a "sore" on the right leg.

She stated that 4 months prior to admission, following a normal, uneventful delivery, she developed a profuse purulent vaginal discharge. Shortly thereafter she became aware of recurrent episodes of painful stiffness and swelling of both elbows and of the left wrist. She also noted a painful pitting edema of the left leg. One month before admission she developed a tender swelling over the lateral surface of the right tibia. The swelling ruptured spontaneously and drained a sanguineopurulent material. Following drainage the area began to develop exuberant granulation tissue. Generalized cramping lower abdominal pain had been present since delivery but recently had become more severe. There were generalized weakness, malaise, anorexia, and a 38 pound weight loss since delivery.

The family history was noncontributory. The only pertinent fact in her past history was that at 5 years of age she had "draining glands" of the neck. These had healed spontaneously and the exact cause was never determined.

Physical examination showed a lethargic, thin, emaciated, dehydrated Negro woman (Fig. 1) with a temperature of 38° C. The scleras were icteric. There were soft, fluctuant, tender swellings over both elbows and the right wrist. Because of some fixation and exquisite pain none of the joints could be moved. The granulating area over the right tibia measured 10 by 7 cm. (Fig. 1). Pelvic examination disclosed an exophytic, granular, bleeding lesion which filled the entire upper vagina and obscured the cervix. The lesion extended through the left vaginal fornix into the left adnexal area almost to the pelvic wall. There were marked thickening and induration on both sides of the pelvis. The hemoglobin was 6.5 Gm. and the white blood cell count 11,600, with the differential count showing a marked shift to the left. Skin tests for the common systemic fungi were negative. Serologic tests for syphilis were negative. The tuberculin test was weakly positive

at a dilution of 1:1,000. Papanicolaou smears from the cervical and leg lesions showed no evidence of carcinoma but contained many large mononuclear cells with intracytoplasmic inclusion bodies. These were identified by the cytologist as Donovan bodies (Fig. 2). Fresh tissue smears stained with Wilson's stain showed innumerable Donovan bodies.

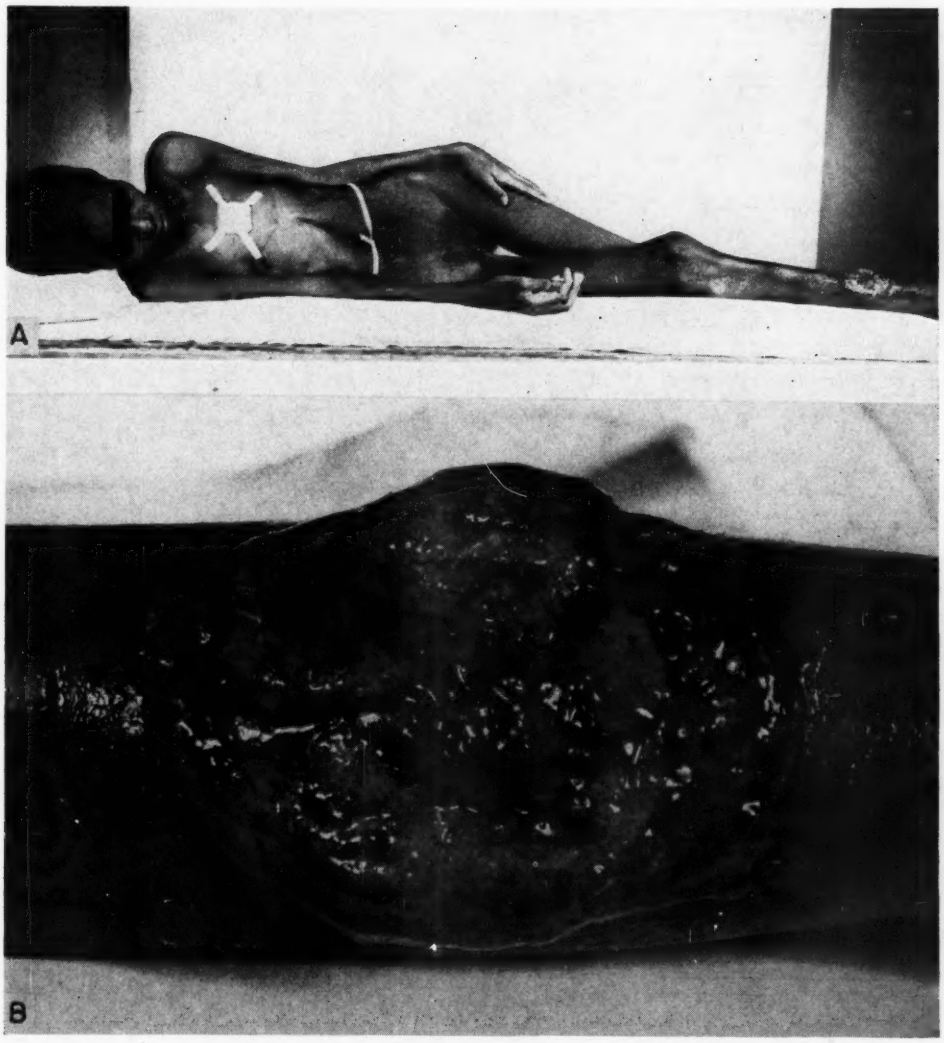

Fig. 1.—*A*, The patient as she appeared shortly after admission to hospital. Cachexia is marked.
B, This lesion, overlying the right tibia, measured 7 by 10 cm.

X-ray examination showed the characteristic osteolytic lesions of the right tibia in the lower third underlying the granulomatous lesion and also in the upper third where the skin was still intact. Similar, but smaller lesions were noted in the right radius. No sequestration or involucrum formation was seen.

The blood chemistry determinations were essentially normal with the exception of the total proteins which were 7.9 Gm. per cent. The albumin fraction was 3.1, and the globulin fraction 4.8, with an A/G ratio of 0.6. Plasma and serum electrophoretic studies indicated the hypergammaglobulinemia, but were not otherwise specific.

The sternal bone marrow aspirate was abnormal in that numerous plasma cells were found. Donovan bodies could not be demonstrated in the sternal marrow. Routine bone marrow cultures for bacteria, fungi, and mycobacteria were negative. No attempt was made to culture *Donovania granulomatis.*

Bone biopsy taken from an area on the right tibia where the overlying skin was intact revealed numerous Donovan bodies.

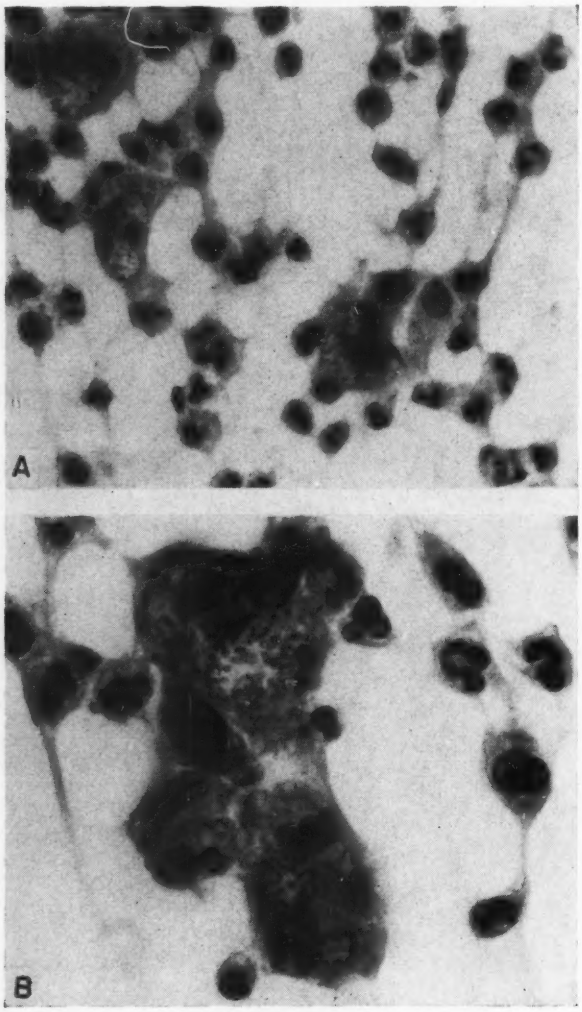

Fig. 2.—Donovan bodies recognized in the Papanicolaou smear. (*A*, ×670; reduced ¼. *B*, ×1060; reduced ¼.)

A diagnosis of disseminated granuloma inguinale was made and definitive therapy started within 24 hours after admission. Tetracycline, 500 mg. twice a day, intravenously for 3 days, was given, and thereafter it was given orally, 2 Gm. daily, for a total of 76 Gm. The patient tolerated the therapy well and no side effects referable to toxicity of the drug were noted. In addition she was given a high-protein diet with between-meal feedings and supplemental iron and vitamin therapy. No other treatment was given. Subjective improvement was rapid. Within 7 days after admission she became afebrile and remained so for the rest of the hospital stay. Complete mobility of the fixed joints was restored in

14 days. The lesions of the cervix and leg, however, were slower in healing. The elbow and wrist swellings became nontender but persisted for 4 weeks. Repeat smears of the cervical and leg lesions showed that the Donovan bodies disappeared in fourteen days.

After 69 hospital days all of the visible lesions had shown marked regression and had remained negative for Donovan bodies. At the time of her discharge from the hospital the cervix was covered with fine feathery granulation tissue. The parametria were not completely free but had much less involvement. The leg lesion had been reduced to approximately one-half its original size and some healing of the bone was evident by x-ray. During her hospital stay she had regained 13 pounds (Fig. 3). The patient was discharged from the hospital on March 23, 1955, for follow-up in the outpatient clinic. All therapy was discontinued.

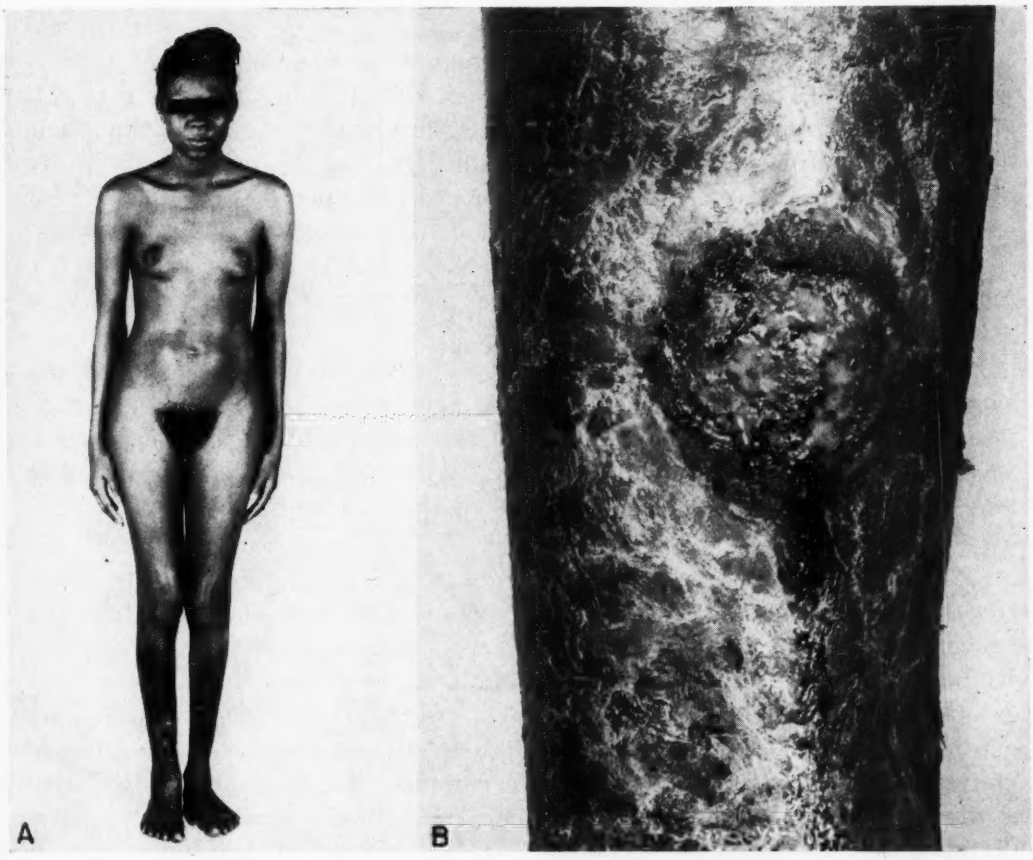

Fig. 3.—*A*, The same patient as in Fig. 1 shortly before discharge from hospital. *B*, Marked regression of the leg lesion.

On June 24, 1955, approximately 3 months later, she returned to the hospital for her first follow-up examination. At this time she had no complaints and had gained 29 pounds since her hospitalization. The leg lesion was now only 2 by 3 cm. in size. Healing of all the bone lesions was evident by x-ray. Pelvic examination showed only slight paracervical induration on the left. The cervix showed a 1 cm. area of granulation tissue. All joints had remained freely movable without pain or swelling. Her menstrual function was normal. The cervical and leg lesions were still negative for Donovan bodies.

Since the patient lived in a distant town and was in poor financial circumstances, we have been unable to get her to return for further examinations and studies. In view

of the completely negative microscopic findings three months after completion of all therapy and from the information we have been able to obtain from the local health authorities, it is believed that she has remained well.

Comment

Extragenital granuloma inguinale is a relatively common lesion and does not seem to be associated with age, sex, or parity of the individual. Examination of the well-documented reports of patients with the disseminated form of the disease shows fairly conclusively that this type of spread is usually, if not always, secondary to lesions of the cervix uteri. It also appears that pregnancy is a predisposing factor in facilitating hematogenous spread in patients with these lesions.

All 7 patients previously reported upon in a well-documented manner were females. Six were Negroes and in one report from India the race was not definitely stated. All had lesions of the cervix save one patient in whom no specific mention of the cervix was made. In 3 of the patients, as in our own, dissemination seemed to be associated with either a term delivery or an abortion. In 3 other patients there was no mention of pregnancy or parity. In only one patient was it possible to be certain that pregnancy was not a factor because a supracervical hysterectomy had been done approximately 10 years before.

In our patient it seems fairly obvious that pelvic and hematogenous spread followed a term delivery. It had been noted at least 2 weeks ante partum that this patient had a large cauliflower-like mass on the cervix which was still present at the time of delivery. Although it was not subjected to biopsy at that time, it seems likely that she had an undiagnosed granuloma inguinale of the cervix.

The response of our patient to therapy was dramatic in the relief of the constitutional symptoms which were quite severe. Marked debility and emaciation seem to form an integral part of the clinical picture in the disseminated form of granuloma inguinale. It is our feeling that tetracycline* is as effective as chlortetracycline or oxytetracycline, and has the added advantage of lessened toxicity when administered over a relatively long period of time to poorly nourished, debilitated patients. Furthermore, we feel that in disseminated granuloma therapy should be continued for a short time after disappearance of the Donovan bodies from the lesions. Thereafter it may be stopped and healing should continue. Regression of the metastatic lesions is notoriously slow and this is particularly true when bone is involved. Surgical excision of the metastatic lesions does not seem to offer any substantial advantage and, in fact, under some circumstances may actually be detrimental. The prognosis, however, should be excellent if treatment is prompt, vigorous, and sustained.

Summary

1. A case is presented of granuloma inguinale disseminated by the hematogenous route.

*The tetracycline (Achromycin) used in treating this patient was supplied by Lederle Laboratories Division, American Cyanamid Company.

2. To our knowledge this is the first patient with this form of granuloma inguinale successfully treated with tetracycline.

3. All previous well-documented case reports were reviewed.

4. Thus far, all the patients reported have been females.

5. Seven of the 8 patients had known cervical granuloma. The remaining report makes no specific mention of cervical involvement. In only one case is it possible to be certain that pregnancy did not play a part in the hematogenous spread of the disease.

6. Severe constitutional symptoms with marked debility and cachexia are serious features of this sometimes fatal disease.

TABLE I. DISSEMINATED GRANULOMA INGUINALE, SUMMARY

AUTHOR	RACE	SEX	INVOLVEMENT OF CERVIX	ASSOCIATION WITH PREGNANCY
Lyford, Scott, and Johnson[14]	Negro	F	No mention	No mention
Paggi and Hull[19]	Negro	F	Yes	No mention
Palik and Schenken[20]	Negro	F	Yes	No mention
Rhinehart and Bauer[25]	Negro	F	Yes	No
Packer, Turner and Dulaney[18]	Negro	F	Yes	Yes
Lipp and Bibby[13]	Negro	F	Yes	No mention
Rajam, Rangiah, and Anguli[24]	Native of India	F	Yes	Yes
Present authors	Negro	F	Yes	Yes

References

1. Anderson, K.: Science **97**: 560, 1943.
2. Anderson, K., DeMonbreun, W. A., and Goodpasture, E. W.: J. Exper. Med. **81**: 25, 1945.
3. Arnell, R. E., and Potekin, J. S.: AM. J. OBST. & GYNEC. **39**: 626, 1940.
4. Becker, S. W.: Discussion of Greenblatt et al.[10]
5. Carter, B., Jones, C. P., and Thomas, W. L.: J. Infect. Dis. **64**: 314, 1939.
6. Dienst, R. B., Greenblatt, R. B., and Sanderson, E. S.: J. Infect. Dis. **62**: 112, 1938.
7. Donovan, C.: Indian M. Gaz. **39**: 321, 1904.
8. Donovan, C.: Indian M. Gaz. **40**: 11, 1905.
9. Gardner, G. H.: in Kelly, Howard A., editor: Gynecology, New York, 1928, D. Appleton Century Company.
10. Greenblatt, R. B., Dienst, R. B., Pund, E. R., and Torpin, R.: J. A. M. A. **113**: 1109, 1939.
11. Greenblatt, R. B., Pund, E. R., Sanderson, E. S., Torpin, R., and Dienst, R. B.: Public Health Service Publication No. 255, Washington, 1953, Superintendent of Documents, Government Printing Office.
12. Greenblatt, R. B., Torpin, R., and Pund, E. R.: A. M. A. Arch. Dermat. & Syph. **33**: 338, 1938.
13. Lipp, R. G., and Bibby, D. E.: West. J. Surg. **58**: 173, 1950.
14. Lyford, John, III, Scott, R. B., and Johnson, R. W., Jr.: Am. J. Syph., Gonorr. & Ven. Dis. **28**: 588, 1944.
15. Mayer, M., and da Rocha Lima, H.: Handb. Hautund. Geschlechtskr. **21**: 433, 1926.
16. McGee, W. B.: AM. J. OBST. & GYNEC. **28**: 244, 1934.
17. McLeod, K.: Indian M. Gaz. **17**: 121, 1882.
18. Packer, H., Turner, H. B., and Dulaney, A. D.: J. A. M. A. **136**: 327, 1948.
19. Paggi, L. C., and Hull, E.: Ann. Int. Med. **20**: 686, 1944.
20. Palik, E., and Schenken, J. R.: Am. J. Clin. Path. **15**: 419, 1945.
21. Pariser, M., and Beerman, H.: Am. J. M. Sc. **208**: 547, 1944.
22. Pund, E. R., and Greenblatt, R. B.: J. A. M. A. **108**: 1401, 1937.
23. Pund, E. R., and McInnes, G. F.: Clinics **3**: 221, 1944.
24. Rajam, R. V., Rangiah, P. N., and Anguli, V. C.: Brit. J. Ven. Dis. **30**: 73, 1954.
25. Rhinehart, W. J., and Bauer, J. T.: Am. J. Roentgenol. **57**: 562, 1947.
26. Sheldon, W. H., Thebaut, B. R., Haymen, A., and Wall, M. J.: Am. J. M. Sc. **210**: 237, 1945.
27. Thierfelder, M. V.: Arch. f. Schiffs- u. Tropen-Hyg. **29**: 690, 1925.

CARCINOMA IN SITU AND THE ROLE OF CYTOLOGY IN ITS DETECTION*

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THERE have been a great number of articles written about the use of the vaginal tract smear in the detection of preinvasive lesions of the cervix that would otherwise have gone undetected.[1-9]

In a recent review of the carcinoma in situ cases at Walter Reed Army Hospital, records for the 5 year period from January, 1951, through January, 1955, were analyzed to determine just what role the vaginal tract smear had played as the initiating factor in detecting lesions that would otherwise have been missed. The term "initiating factor" is used because the cytological smear is not a diagnostic agent but merely a screening procedure indicating to the clinician that further histopathological studies should be made.

In this study, 84 cases of carcinoma in situ were reviewed. Seventy-two of the 84 patients had positive cytological smears as the first step that led to the final confirming diagnosis.

Classification of the Papanicolaou Smear.—The Papanicolaou classification (Table I) is used in grading cytological smears. Class III, IV, and V cytological smears are considered positive and further diagnostic procedures are routinely carried out. The Class III smear is not cytologically positive, however, but is considered clinically positive. In a recent survey of the cytological smears taken in a 2 year period on 13,501 patients, it was found that 9 out of 10 patients who had a Class V smear would, on further study, have a genital tract malignancy. In Class IV smears the incidence was 4 out of 10, and in Class III smears, it was 2 to 3 out of 10.

Table I. Classification of the Papanicolaou Smear

Class I.	No atypical cells seen.
Class II.	No evidence of malignant neoplasia in cells which may otherwise be atypical.
Class III.	Cell changes suspicious of cancer (borderline).
Class IV.	An element of doubt persists in spite of fairly conclusive evidence of cancer. Doubt is based either upon the scarcity of cells present, or upon lack of conclusive characteristics. This is classified as positive for cancer.
Class V.	Cells characteristic of a malignant neoplasm.

*Presented at a meeting of the Continental Gynecological Society at Walter Reed Army Hospital on May 25, 1956.

Patients with a positive cytological smear, after a repeat and confirming smear, are admitted for a Schiller test, fractional dilatation and curettage, and a wide cold-knife conization of the cervix.

Distribution of Presenting Symptoms.—It is interesting to note the number of patients who present themselves for a "regular check-up" or for a "cancer smear" or because of various symptoms (Fig. 1). It has long been a policy that all patients for examination, either on an inpatient or outpatient status, will have cytological smears taken, regardless of the clinical appearance of the cervix or of the presenting symptoms. After these patients have been cleared, they are advised to have a routine examination and repeat cytological smears every 6 months unless symptoms dictate otherwise.

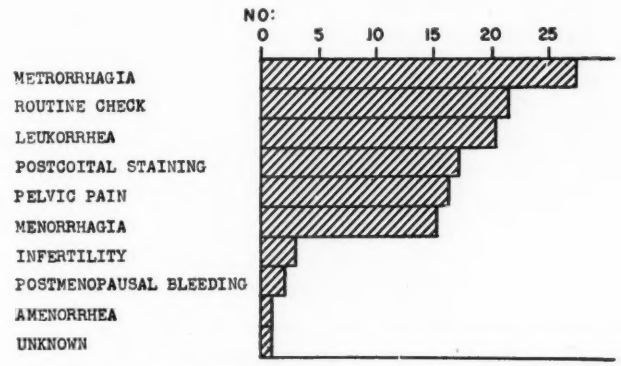

Fig. 1.—Distribution of the presenting symptoms on initial examinations.

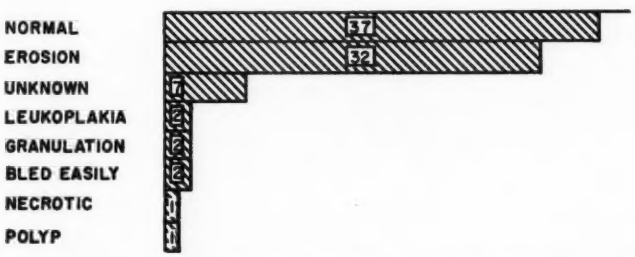

Fig. 2.—Clinical evaluation of the cervix on initial examination.

Clinical Evaluation of the Cervix on Initial Examination.—In 37 of the 84 cases the examining physician classified the cervix as normal (Fig. 2). In the absence of any detectable pathological condition, it is unlikely that these cervices would have been histologically examined. If a quadrant biopsy was done, it is not unreasonable to assume that the area containing the lesion may have been missed with the punch biopsy forceps. Cytological interpretations, however, represent evaluations on cells that have been exfoliated from a large surface area.

Distribution of Papanicolaou Smears in 72 Cases of Carcinoma in Situ.—Of the 72 cases of carcinoma in situ only 3 had had negative Papanicolaou smears (Fig. 3). These particular cases were reviewed, but the classification could not be altered. It should be noted here that the cytologist can only interpret the material presented, and if the physician fails to take an adequate smear the report will be false negative. At Walter Reed Army Hospital

the swab technique with a cotton-tip applicator is used to take both an endocervical and a vaginal smear. The endocervical smear is the more important of the two. If these smears are not adequate, the cytologists will advise that repeat smears be taken.

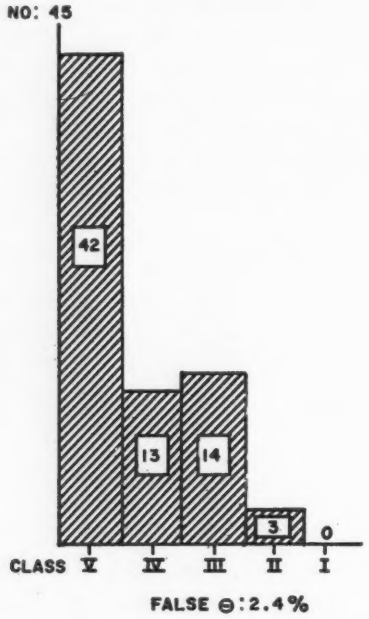

Fig. 3.—Distribution of Papanicolaou smears in 72 cases of carcinoma in situ.

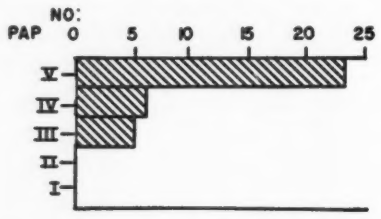

Fig. 4.—The normal cervix: 34 cases with distribution of Papanicolaou smears.

Classification of Papanicolaou Smears in 34 Cases With Normal-Appearing Cervix.—When evaluating the results of vaginal cytology and carcinoma in situ, one cannot help being impressed by the fact that one of its major uses is in the detection of totally unsuspected cervical carcinoma. Thirty-four smears were taken on 37 patients in whom the cervix appeared normal (Fig. 4). The 3 patients in whom no cytological smears were taken were patients operated on elsewhere for lesions not involving the cervix. The diagnosis of carcinoma in situ was made on pathological examination of the uterus. There was not one false negative smear in this particular group and, although this is an admittedly small number, these 34 cases more than exemplify the efficacy of the cytological smear as a routine screening procedure in detecting unsuspected cervical cancer.

Summary

1. Eighty-four cases of carcinoma in situ, with reference to determining the role of cytoanalysis, have been reviewed. Of the 72 smears taken on these

patients, there were 3 false negatives, making the rate of false negatives 2.4 per cent.

2. There were 34 cases, or 40.5 per cent of the cases reviewed, in which a positive smear was the initiating step in establishing a diagnosis that would otherwise have been *totally* unsuspected.

3. The normal-appearing cervix offers the greatest challenge to early detection of unsuspected cervical carcinoma, and this is one of the values of the cytological smear.

References

1. Anderson, H. F., Grant, M. P. S., McBryde, P. M., and Cockburn, M. K.: J. Obst. & Gynaec. Brit. Emp. **60**: 345, 1953.
2. Fennell, Robert H.: Cancer **8**: 302, 1955.
3. Fennell, Robert H., and Graham, Ruth M.: Cancer **8**: 310, 1955.
4. Fennell, Robert H., Jr., and Castleman, Benjamin: **252**: 985 and 1032, 1953.
5. Koss, Leopold G., and Durfee, Grace R.: Cancer **8**: 295-301, 1955.
6. Nesbitt, R. E., and Brack, C. B.: J. A. M. A. **161**: 183, 1956.
7. Riva, H. L., and Breen, J. L.: Exfoliative Cytology in the Detection of Pelvic Malignancy, Armed Forces Seminar, April, 1956, Walter Reed Army Institute of Research.
8. Tombard, Herbert L., et al.: New England J. Med. **246**: 523, 1952.
9. Wied, George L.: Am. J. Clin. Path. **25**: 742, 1955.

GLYCOGEN IN THE SQUAMOUS EPITHELIUM OF THE CERVIX UTERI*

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IT HAS been known for many years that the squamous epithelium of the human cervix contains glycogen. Schiller,[1] in 1933, in his classical article on early diagnosis of carcinoma of the cervix, noted the presence of glycogen in the superficial layers of normal squamous epithelium and the lack of it in carcinoma. His method of vital staining with iodine solution to identify areas for biopsy is well known.

More recently, glycogen has been demonstrated by a variety of histochemical techniques, among which the periodic acid-Schiff method, through the efforts of McManus[2] and of Hotchkiss,[3] has become a reliable way of demonstrating glycogen in fixed tissue.

Not a little attention has been given to glycogen in the squamous epithelia in general and in the cervix in particular. Foraker[4] has studied a variety of squamous carcinomas stained for glycogen. Biggers[5] investigated the mouse vagina with the PAS (periodic acid-Schiff) method and gave an account of the PAS positive substances he found in the epithelium. Scothorne and Scothorne[6] studied the glycogen content of human skin autografts and outlined the current views on the part glycogen plays in epithelial metabolism. Wislocki, Bunting, and Dempsey[7] mentioned its presence in the exocervix in their specimens. Wheeler and Danziger[8] have recently described a series of normal cervices, using a variety of histochemical procedures.

McManus and Findley[9] in 1949 made a study of the glycogen in carcinoma in situ of the cervix. They obtained the paraffin-embedded blocks of tissue from 8 cases of carcinoma in situ of the cervix and stained further sections by the PAS method. They concluded that carcinoma in situ contains no glycogen. Foraker[10] has recently reported on biopsies from 21 invasive carcinomas of the cervix stained for glycogen. Thirteen showed some degree of glycogen staining, especially in areas of greater differentiation. Although he had no in situ lesions in his reported series he mentions having seen small amounts of glycogen in some of the carcinomas in situ he has examined. Lee[11] recently studied 11 cases of carcinoma in situ, in all but one of which he saw glycogen, albeit in diminished amounts.

*This work was made possible by a grant from the National Cancer Institute of Canada.

It was with this groundwork in mind that we resolved to demonstrate the presence of glycogen in a series of cervical biopsy specimens.

Material

In our clinic it is routine practice to follow the report of suspicious cytological findings in the cervix by a ring biopsy. The method has been described by Latour.[12] We chose the ring biopsy material for our study because the epithelium runs the gamut from normal through invasive carcinoma and because the greatest number of cases of anaplasia and carcinomas in situ are found here.

Between Jan. 1, 1955, and March 31, 1956, there were 69 ring biopsies performed, of which 33 showed no malignancy and 36 showed malignancy; 14 of these were in situ carcinomas. We received 49 of these specimens, of which 19 showed no malignancy and 30 showed malignancy, 12 being in situ lesions.

Method

The biopsy is immediately immersed in ice-cold Rossman's[13] fluid and allowed to harden for several hours. Then it is cut into many radial segments and returned to the fixative for a total fixing time of twenty-four hours. The segments are then dehydrated and embedded in one paraffin block and three serial sections are cut. One of these is stained by our routine hematoxylin and eosin technique, the second by the PAS method of Hotchkiss[3] for glycogen, and the third is incubated with salivary diastase before being stained by the PAS technique, and serves as a control.

The periodic acid-Schiff reaction has been recognized since its introduction by Hotchkiss in 1948 as one of several good methods of identifying glycogen in histological section. It shares, with other methods, a lack of specificity for glycogen but this difficulty can be overcome by incubating control sections with diastase before performing the PAS reaction. Diastase digests only the glycogen and leaves the other substances free to react. Our diastase is obtained from human sputum from a tested source.

Observations

In the normal squamous epithelium (Fig. 1), the periodic acid-Schiff reaction shows the basement membrane, the cell membranes, and the intercellular bridges as thin, sharply defined, red-brown structures. The basal layer of cells shows a homogeneous bright yellow cytoplasm and scarcely distinguishable yellow nuclei. Several layers of parabasal cells show the same features but are sprinkled with fine, dense carmine granules, or with a homogeneous, lightly staining carmine halo. Further toward the surface, the carmine material becomes denser and fills more of the cytoplasm. In the precornified layer, where the cells are elongated and flat, the carmine material appears as discrete lozenges lying on one another. At the surface the lack of cytoplasm makes the carmine concentration diminish and the red-brown cell membranes form a thick compact surface layer.

In the endocervical glands (Fig. 4), the columnar cells, on a thin red-brown basement membrane, are partly filled with dense carmine material in a granular or homogeneous form. The lumen contains a few globules of the material free or attached to the surface of the cells.

In the sputum-treated control (Fig. 2), the squamous epithelium shows the same features as the PAS section except for the complete absence of cytoplasmic carmine. The endocervical glands (not illustrated) still show the

Fig. 1.

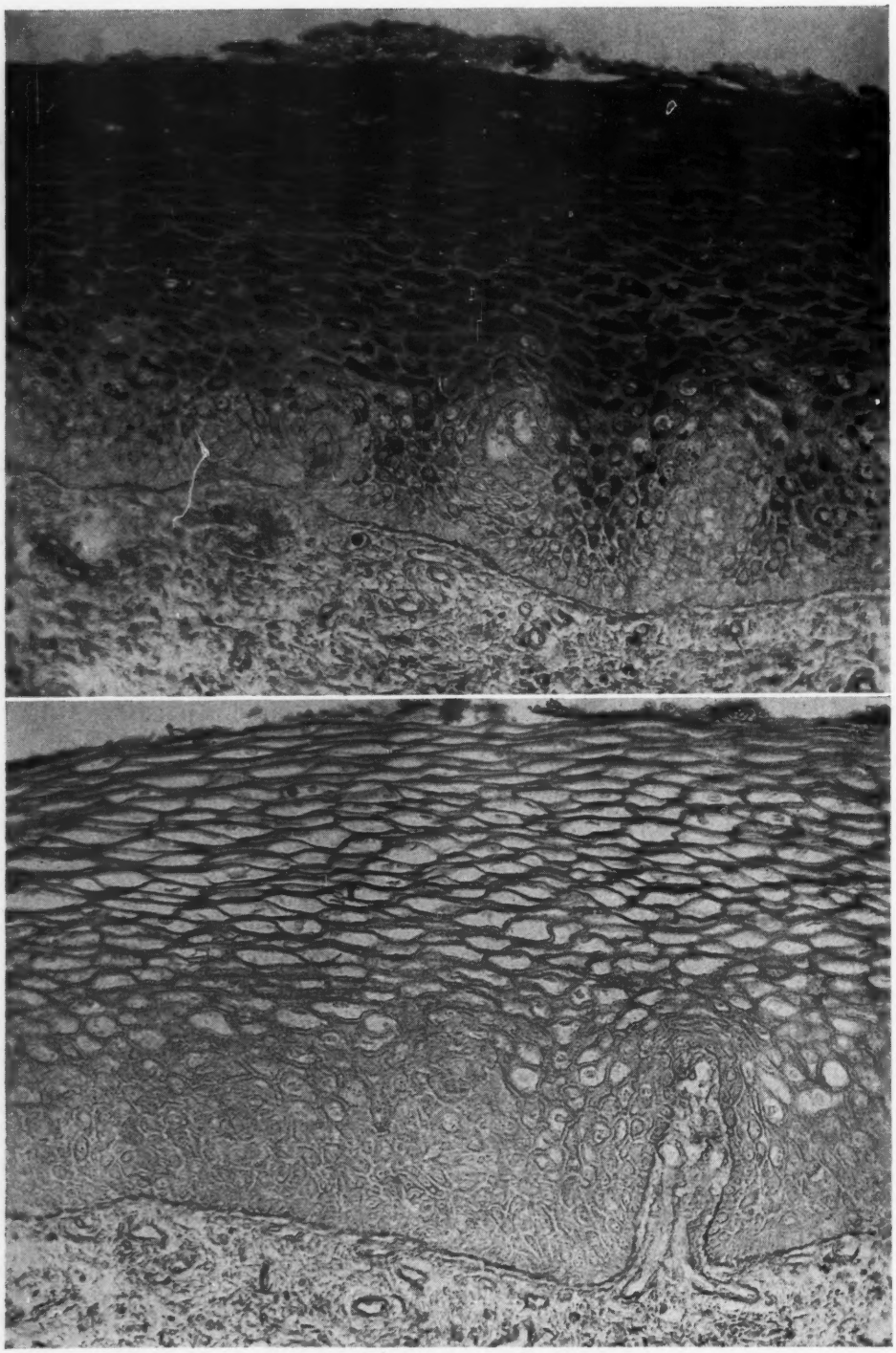
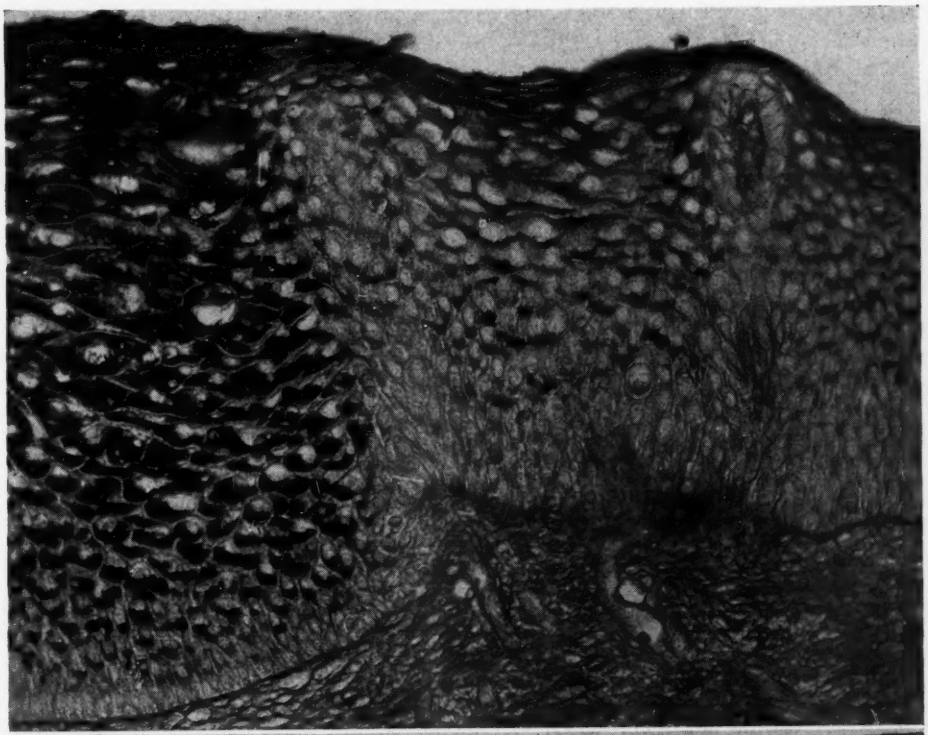


Fig. 2.

Fig. 1.—Normal cervical squamous epithelium. (Periodic acid-Schiff stain. ×225; reduced ⅙.)
Fig. 2.—Normal cervical squamous epithelium. (Periodic acid-Schiff control. ×225; reduced ⅙.)

Fig. 3.



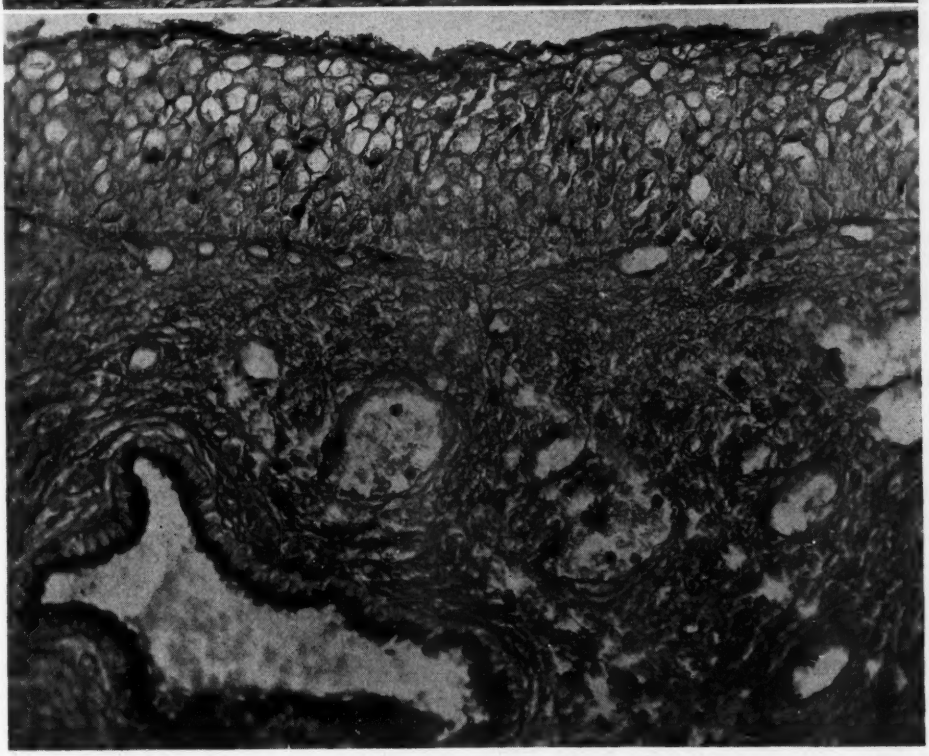


Fig. 4.

Fig. 3.—Moderate anaplasia of the cervix. (Periodic acid-Schiff stain. ×225; reduced ⅙.)
Fig. 4.—Carcinoma in situ of the cervix. (Periodic acid-Schiff stain. ×225; reduced ⅙.)

same carmine material they did in the PAS section. Thus we see that the carmine material in the squamous cells is glycogen while all other carmine material is not.

We occasionally observed specimens in which the degree of color reaction varied markedly from that usually seen. In some it was so deep as to render borders of the cells indistinguishable, while in others it was so light that color could hardly be identified, even in tissue we knew to be normal. While the density varied, the distribution of carmine material remained typical. We are at a loss to account for this variation; we note that it occurred also in the endometrial sections of Payne and Latour,[14] who demonstrated a poor correlation between density of stain and quantitative glycogen content.

Squamous metaplasia and epidermidalization are terms now agreed to describe an identical pathological morphology. Whether on the surface or in the endocervical glands, it was generally observed that the more active the process, the less glycogen was found.

The lack of differentiation of squamous epithelial cells taking part in repair is sometimes called anaplasia of repair. In our material we have observed that the glycogen is scanty if not absent in the less mature cells.

In respect to hyperkeratosis we feel that the epithelium lying beneath the abnormal surface is a normal one and should show a normal distribution of glycogen. We have not seen enough suitable examples to substantiate this, however. The keratotic layers themselves show the PAS positive, saliva-resistant material common to the cornified layers of all our sections. The keratin granules stain in a similar way.

Our concept of leukoplakia is basically that of hyperkeratosis overlying an epithelium with some degree of anaplasia. Our specimens show the lack of glycogen which we have come to expect of anaplasia in specimens with no hyperkeratosis.

One lesion of the squamous epithelium is in some centers called basal-cell hyperactivity, in others cell atypism, and, in still others, as in our own, anaplasia. We refer to the loss of differentiation of the cells in the partial or whole thickness of the epithelium to a degree short of that typical of carcinoma in situ. We usually classify anaplasia as mild, moderate, or severe for purposes of discussion, recognizing, however, no sharp divisions between these classes.

Our benign specimens ran the gamut from very mild anaplasia to others very difficult to distinguish from carcinoma in situ. The PAS slides showed a tendency to a decrease in the amount of glycogen as the anaplasia became more severe, but it was always possible to detect some glycogen in lesions we called anaplasia, even when we reviewed our sections as virtual "unknowns." Fig. 3, which illustrates a moderate degree of anaplasia, shows the comparative decrease in glycogen.

In carcinoma in situ the neoplastic epithelium shows in all our specimens a complete lack of glycogen. Fig. 4 shows an area of surface carcinoma in situ.

None of the specimens of invasive carcinoma we have examined contain any glycogen. We note the discrepancy between the findings of Lee and of Foraker and our own. Concerning the carcinomas in situ, we feel that our failure to detect glycogen in a lesion which others have found to contain small amounts may be a reflection on our conservatism in making this diagnosis. As to our failure to find glycogen in invasive carcinoma, the method of obtaining our material gave us access to only the early invasive lesions. We have not studied the more advanced lesions in which the more mature areas studied by Foraker occur.

Conclusions

By the use of a three-slide serial-section technique with hematoxylin and eosin, periodic acid-Schiff, and a control, we feel we have been able to identify glycogen and describe its distribution in the squamous epithelium of the cervix.

Glycogen is present in the normal squamous epithelium in relatively large amounts.

The degree of activity of the squamous cell expressed in routine stains as differentiation is expressed in the PAS stains by the amount of glycogen present. The more active the cell, the less differentiation and the less glycogen there is. This is true of the basal cell in normal epithelium, of the cells of squamous metaplasia, of all grades of anaplasia, and of neoplasia.

There is no evidence that changes in the distribution or amount of glycogen precede changes in the morphology visible in any good routinely stained section. On the other hand, the parallel disappearance of glycogen with the appearance of neoplasia sometimes upholds a diagnosis of carcinoma that would be difficult to make on morphology alone.

We feel that the disappearance of glycogen through all grades of anaplasia to its absence in neoplasia is further evidence justifying the growing concept of cervical epithelium gradually dedifferentiating until it becomes carcinoma in situ.

References

1. Schiller, Walter: Surg., Gynec. & Obst. **56**: 210, 1933.
2. McManus, J. F. A.: Nature **158**: 202, 1946.
3. Hotchkiss, R. D.: Arch. Biochem. **16**: 131, 1948.
4. Foraker, A. G.: Cancer **9**: 367, 1956.
5. Biggers, J. D.: J. Anat. **87**: 327, 1953.
6. Scothorne, R. J., and Scothorne, A. W.: J. Anat. **87**: 22, 1953.
7. Wislocki, G. B., Bunting, H., and Dempsey, E. W.: The Chemical Histology of the Human Uterine Cervix With Supplementary Notes on the Endometrium. In Earle T. Engle, editor: Menstruation and Its Disorders, Springfield, Ill., 1950, Charles C Thomas, Publisher.
8. Wheeler, J. D., and Danziger, Sara: Obst. & Gynec. **5**: 739, 1955.
9. McManus, J. F. A., and Findley, L.: Surg., Gynec. & Obst. **89**: 616, 1949.
10. Foraker, A. G.: Am. J. Obst. & Gynec. **72**: 400, 1956.
11. Lee, L. E., Jr.: Surg., Gynec. & Obst. **102**: 677, 1956.
12. Latour, J. P. A.: Surg., Gynec. & Obst. **94**: 270, 1952.
13. Rossman, I.: Am. J. Anat. **66**: 277, 1940.
14. Payne, H. W., and Latour, J. P. A: J. Clin. Endocrinol. & Metab. **15**: 1106, 1955.

RANDOM INGUINAL NODE BIOPSY AND PERITONEAL FLUID STUDY IN OVARIAN CANCER*†

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OF ALL cancers of the pelvis, the clinical diagnosis of ovarian carcinoma is the most difficult. In many cases the patient does not seek medical care until late in the course of the disease when distant metastases are already present or the local spread makes even the most extensive surgery impossible. The best results obtained in dealing with ovarian carcinoma are in the cases in which operation is performed for other pelvic disease and an early cancer of the ovary discovered.

Present-day therapy, which for the most part in this country is surgical, has little to offer the patient when spread beyond the ovarian capsule has occurred. Radiation therapy in itself is seldom curative, although occasionally good results are obtained in the more radiosensitive tumors.

Many investigators have had the experience of performing laparotomy for adnexal disease and, finding a nonresectable ovarian cancer, of making a re-exploration in the same patient after a course of deep pelvic x-ray therapy and finding the tumor at this time amenable to extirpation.

Because the results in primary surgery or radiation therapy alone are so discouraging, and because some cancers are amenable to surgery only after deep pelvic x-ray, the Department of Gynecology at Tulane University and the Tulane Unit, Charity Hospital, began in 1951 to utilize random inguinal node biopsy and cell-block studies of peritoneal fluid in all cases of suspected ovarian cancer. We attempted, in this manner, to establish the diagnosis of ovarian cancer prior to any attempt at definitive surgery. If the diagnosis is made by these methods, a preoperative course of deep pelvic x-ray is given and the patient is operated upon at a later date.

Thus, in addition to the usual preoperative studies of the bowel, urinary tract, and cardiovascular systems, a cell-block study of paracentesis or culdocentesis fluid and an inguinal node biopsy are performed.

*Aided by a grant from the Ex-Residents and Fellows Research Fund.

†Presented at the Regular Meeting of the New Orleans Gynecological and Obstetrical Society on Nov. 20, 1956.

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Material and Methods

The technique of paracentesis and culdocentesis needs no explanation.

In the performance of the node biopsy, both inguinal regions are carefully palpated, and any palpable lymph nodes removed. If none are palpable an incision is made in the inguinal region on one side or the other, and, after the superficial fascia is passed, nodes are usually easily palpable. This procedure is performed without difficulty under local anesthesia. It is simple and safe if caution is exercised to avoid the large vessels in this region. It can be performed on the ward or in the office and requires only 10 to 15 minutes. The delay until receipt of the pathologic diagnosis is usually taken up with other diagnostic procedures. To date we have had no complications resulting from this method of node biopsy. This report does not include all cases of ovarian cancer seen since 1951, but a series of 28 patients in whom either abdominal fluid studies or inguinal node biopsy or both were performed. The following observations are important mainly in prognosis, but other interesting relationships are apparent.

Results

A total of 35 specimens of abdominal fluid obtained by paracentesis or culdocentesis from 24 patients was submitted for study. Malignant cells were found in 13 specimens. Three different samples of fluid were examined from 3 patients and none was found to be positive. In 5 cases two samples each were submitted and, on the second specimen, 2 patients were found to have malignant cells in the fluid. In the cases in which only one specimen was submitted 11 of the 16 were positive (Table I).

Lymph nodes were found to contain metastatic carcinoma in 10 of the 17 cases in which this procedure was carried out. Thus, there were positive nodes in 59 per cent of these 17 cases. Of the 24 patients in whom fluid studies were done 13, or 54 per cent, had positive fluid. This includes 2 patients who were found to have malignant cells in the second specimen studied (Table I).

TABLE I. POSITIVE AND NEGATIVE FINDINGS

	NO. OF CASES	POSITIVE		NEGATIVE		% FALSE
		NO.	%	NO.	%	
Paracentesis or culdocentesis	24	13		22		
Done 3 times	3	0		9		
Done twice	5	2		8		
Done once	16	11		5		
Inguinal node biopsy	17	10	59	7		
Fluid studies	24	13	54	13		
Positive diagnosis ovarian carcinoma*:						
Node study	16			7		44
Fluid study	22			10		45

*Proved by operation or autopsy.

There were no "false positive" fluids or nodes in the cases in which surgical or autopsy confirmation was later available. A proved diagnosis of ovarian cancer was made in 16 of the 17 cases in which node biopsy was performed. Seven of these 16 patients did not have lymph node metastases. Thus, there were 44 per cent "false negative" nodes. This obviously does not mean the procedure is without merit, but, as will be shown, node metastases are present only in the late stages of the disease.

A proved diagnosis of ovarian carcinoma was made in 22 of the 24 cases in which fluid studies were done. In 10 of these 22 cases, malignant cells were not found in the fluid examined. Thus, there were 45 per cent "false negative" fluids (Table I).

Fluid or node studies, or both, were done in 28 cases. In the 11 cases where fluid study only was done, 5 were positive, or 45 per cent. Four patients had inguinal node biopsy without examination of the peritoneal fluid. Two of these nodes contained metastatic tumor. When we examine the 13 cases in which both fluid and nodes were examined, it was found that 10, or 77 per cent, had positive nodes or positive fluid or both. If this holds true in future cases of suspected ovarian cancer we should be able to make a preoperative diagnosis of ovarian carcinoma in about 8 out of 10 cases. Preoperative radiation would then be possible and the survival might thus be improved (Table II).

TABLE II. RESULTS

	NO.	NODES		FLUID		POSITIVE NODE AND FLUID	NEGATIVE NODE AND FLUID	% POSITIVE
		POSITIVE	NEGATIVE	POSITIVE	NEGATIVE			
Nodes and fluid in same patient	13	2		2		6	3	77
Fluid study only	11			5	6			45
Node study only	4	2	2					50
Total	28	4	2	7	6	6	3	

Fourteen cases of papillary cystadenocarcinoma were encountered. Nine of the 13 positive fluids were found in patients with this tumor. The other 4 positive fluids were distributed among the other types listed in Table III, which also shows the comparison of the histology of the metastatic lymph nodes and of the specimens obtained at operation or autopsy. The histology is very similar in most of the cases. In contrast to the findings in patients with positive fluids, however, the less differentiated tumors seem to be more prone to lymph node metastases in this small series than are the more differentiated types.

TABLE III. COMPARISON OF FLUID AND BIOPSY WITH OPERATIVE OR AUTOPSY FINDINGS

HISTOLOGIC DIAGNOSIS OF OVARY AT OPERATION OR AUTOPSY	CASES	POSITIVE	HISTOLOGIC DIAGNOSIS OF NODES
Paracentesis or Culdocentesis Fluid.—			
Papillary cystadenocarcinoma	14	9	
Pseudomucinous cystadenocarcinoma	3	1	
Adenocarcinoma	2	1	
Carcinoma, undifferentiated	2	1	
Krukenberg tumor	1	0	
? (no operation or autopsy)	2	1	
Inguinal Node Biopsy.—			
Papillary cystadenocarcinoma	9	5	2 adenocarcinoma 2 papillary adenocarcinoma 1 papillary cystadenocarcinoma
Pseudomucinous cystadenocarcinoma	2	0	None
Adenocarcinoma	3	2	2 anaplastic carcinoma
Carcinoma, undifferentiated	2	2	2 undifferentiated carcinoma
? (no operation or autopsy)	1	1	1 adenocarcinoma

In the 17 cases in which lymph node studies were made, 9 patients had papillary cystadenocarcinomas, 5 of whom had positive nodes. The 2 cases of undifferentiated carcinoma of the ovary showed lymph node metastasis. Two of 3 patients with adenocarcinoma had positive lymph nodes showing anaplastic carcinoma (Table III).

Table IV shows a breakdown of 24 cases in which fluid studies were done. It was possible to perform total hysterectomy and bilateral salpingo-oophorectomy in only 3 of these cases. In only one of these 3 was the tumor found to be confined to the pelvis. All 3 patients had negative lymph nodes, while 2 were found to have malignant cells in the peritoneal fluid. Of the remaining patients, 16 had nonresectable disease at the time of exploratory laparotomy, 3 had no surgery but were autopsied, and 2 had neither surgery nor autopsy.

TABLE IV. OPERATION OR AUTOPSY FLUID STUDY

TYPE	FLUID		NODE	ABDOMINAL METASTASES	LIMITED TO PELVIS
Total hysterectomy, bilateral salpingo-oophorectomy	3	(2+) (1–)	(3–)	2	1
Exploratory laparotomy, biopsy only	16	(7+) (9–)	(4+) (2–)	16	0
Autopsy only	3	(3+)	(3+)	3	0
No operation or autopsy	2	(1+) (1–)	(1+)	?	?
Total	24			21	1

Of the 17 cases in which lymph node studies were made, it was possible to do a total hysterectomy and bilateral salpingo-oophorectomy in 6. The tumor was confined to the pelvis in 3 of these patients. None of these 3 had positive nodes, but one had malignant cells in the peritoneal fluid. Two of the 6 patients who had total hysterectomy and bilateral salpingo-oophorectomy had positive fluid, only one had a positive node (Table V).

TABLE V. OPERATION OR AUTOPSY NODE BIOPSY

TYPE	NODE		FLUID	ABDOMINAL METASTASES	LIMITED TO PELVIS
Total hysterectomy, bilateral salpingo-oophorectomy	6	(1+) (5–)	(2+) (1–)	3	3
Exploratory laparotomy, biopsy only	7	(5+) (2–)	(2+) (4–)	7	0
Autopsy only	3	(3+)	(3+)	3	0
No operation or autopsy	1	(1+)	(1+)	?	?
Total	17			13	3

TABLE VI. PREOPERATIVE RADIATION*

	NO.	POSITIVE NODES AND/OR FLUID IN SAME PATIENT	FLUID STUDY ONLY (POSITIVE)	NODE STUDY ONLY (POSITIVE)	PREOPERATIVE RADIATION
Total hysterectomy, bilateral salpingo-oophorectomy	3	2	0	1	2
Exploratory laparotomy and biopsy only	10	4	5	1	6
Total	13	6	5	2	8

*Includes only patients who had positive nodes and/or fluid, who had surgical exploration.

TABLE VII. SURVIVAL IN RELATION TO POSITIVE STUDIES AND PREOPERATIVE RADIATION*

PATIENT	FLUID	NODE	PREOPERATIVE RADIATION	LIMITED TO PELVIS	EXTENT OF SURGERY	TIME IN MONTHS, DIAGNOSIS TO DEATH	SURVIVAL IN MONTHS, DIAGNOSIS TO LAST FOLLOW-UP	LAST VISIT	REMARKS
No. 4 A. M.	Positive	Not done	Yes	No	Laparotomy	11	–	–	–
No. 5 L. N.	Positive	Not done	Yes	No	Laparotomy	7	–	–	–
No. 20 J. W.	Not done	Positive	Yes	No	Hysterectomy and bilateral salpingo-oophorectomy	–	29	3/54	Recurrence
No. 23 L. G.	Negative	Positive	Yes	No	Laparotomy	5	–	–	–
No. 37 C. D.	Not done	Positive	No	No	Laparotomy	6	–	–	–
No. 44 S. S.	Positive	Not done	No	No	Laparotomy	–	No follow-up		
No. 55 A. P.	Positive	Not done	Yes	No	Laparotomy	–	No follow-up		
No. 57 M.W.	Positive	Negative	Yes	No	Hysterectomy and bilateral salpingo-oophorectomy	–	11	1/55	Recurrence
No. 61 O. J.	Positive	Not done	No	No	Laparotomy	–	8	2/55	Recurrence
No. 63 E. N.	Positive	Positive	No	No	Laparotomy	1	–	–	–
No. 65 A. B.	Positive	Negative	No	Yes	Hysterectomy and bilateral salpingo-oophorectomy	–	13	10/56	No evidence of recurrence
No. 66 E. P.	Positive	Positive	Yes	No	Laparotomy	–	11	10/56	Recurrence
No. 69 V. C.	Negative	Positive	Yes	No	Laparotomy	–	2	11/56	Recurrence

*Includes only patients with positive fluid and/or nodes, who had surgical exploration.

Table VI shows the results with preoperative radiation in patients who had positive nodes and/or peritoneal fluid, and who had surgical exploration. Total hysterectomy and bilateral salpingo-oophorectomy were possible in 3 of these cases, in 2 of which preoperative deep x-ray therapy had been given. Exploratory laparotomy was performed in 10 patients, but the malignancy was unresectable. Six of these 10 had preoperative radiation.

Table VII shows the follow-up in the group in whom exploratory laparotomy was performed after fluid and/or node studies were found to be positive: Five patients had either recurrent or progressive ovarian cancer. Three of these have not been seen in many months and are presumed to have succumbed. One patient who had positive peritoneal fluid and whose disease was resectable is alive without apparent recurrence thirteen months after diagnosis. All the other patients are dead or were alive with recurrent tumor when last seen. The prognosis, therefore, with positive fluid or nodes is very grave, even with preoperative radiation and despite the fact that resection of the tumor is thus made possible.

Comment

Eichner and his co-workers[1, 2] have investigated the spread of pontamine sky blue and direct sky blue dyes following injection of the ovaries with these materials. These investigations were carried out on laboratory animals and then, after the safety of the procedure was established, the dyes were injected into the ovaries of patients at the time of operation. From these experiments, Eichner and his associates concluded that "in general, unblocked ovarian lymphatics follow the course of the ovarian vessels." However, if the uteroovarian and infundibuloplevic ligaments were ligated, followed by injection of the ovary, "most of the dye advanced to the lateral pelvic wall by way of the round ligament," and "a very small amount entered the inguinal canal, but none was ever seen in the inguinal skin." The spread of the dye by this route occurred only when the infundibulopelvic and uteroovarian ligaments were ligated and this method of spread was considered as an alternate or secondary route.

In this series of 28 cases in which inguinal node biopsy and/or cell-block study of peritoneal fluid were performed, 17 patients had inguinal node biopsies. Ten patients were found to have metastatic tumor in a random lymph node removed. All of these patients had advanced ovarian cancer and none of them are alive today without persistent or recurrent ovarian carcinoma. All patients with metastases to the lymph nodes of the inguinal region had concomitant spread of the tumor to the peritoneum, omentum, liver, or other areas in the abdominal cavity. The prognosis when the inguinal nodes contain metastases from ovarian cancer is exceedingly poor.

As is the case with inguinal metastases, the presence of malignant cells free in the peritoneal cavity, as determined by cell-block study of paracentesis or culdocentesis fluid, is likewise a grave prognostic sign. Perhaps with deep pelvic x-ray therapy, surgical extirpation may be made feasible and survival improved even if malignant cells are present free in the peritoneal cavity. This probably will not hold true if inguinal node metastases are present, however.

Conclusions

1. Twenty-eight cases of ovarian cancer were studied by inguinal node biopsy and/or cell-block study of paracentesis or culdocentesis fluid.

2. The prognosis is grave if malignant cells are found in the fluid, and much worse if metastatic ovarian cancer is found in the inguinal lymph nodes.

3. Positive nodes were found in 59 per cent of the cases studied, and positive fluids in 54 per cent of the cases.

4. If both studies are carried out in the same patient, the preoperative diagnosis of ovarian cancer is more likely to be made than if just one of the procedures is carried out.

5. A follow-up of 13 patients in whom positive studies were obtained and in whom surgical exploration was performed is presented.

References

1. Eichner, E., Goldberg, I., and Bove, E. R.: Am. J. Obst. & Gynec. 67: 1277, 1954.
2. Eichner, E., and Bove, E. R.: Obst. & Gynec. 3: 287, 1954.

POSTERIOR COLPOTOMY FOR THE DIAGNOSIS AND TREATMENT OF PELVIC DISEASE*

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BIMANUAL pelvic examination often does not provide enough information to permit the accurate evaluation of pelvic symptoms, particularly when an abnormal condition produces pain or local tenderness. Examination of the anesthetized patient will sometimes clarify the problem but in some it is essential that other methods be utilized.

Most diagnostic problems are concerned with detecting the presence of blood or pus in the pelvic cavity, the differentiation between tubal pregnancy, threatened abortion, and hemorrhage from functional ovarian cysts, the exclusion or diagnosis of salpingitis, and/or similar problems. Needle colpocentesis has been utilized extensively in the diagnosis of tubal pregnancy, but its accuracy leaves much to be desired.[1] If this procedure is to be of positive diagnostic value, blood must be present in the cul-de-sac and the needle must be inserted into the material. A negative needle aspiration proves nothing, however, because there will be no bleeding from an unruptured tubal pregnancy.

If the cul-de-sac is opened, a more accurate appraisal of the pelvic organs can be made,[2] and in many instances definitive surgical procedures such as salpingectomy, oophorectomy, etc., can be completed through the colpotomy incision.[3] Diagnostic colpotomy is particularly helpful in patients suspected of having tubal pregnancy if blood cannot be aspirated from the cul-de-sac, and in those with small adnexal enlargements or unexplained pelvic pain. Any surgeon who is qualified to perform surgical procedures in the pelvis should be able to master the technique of posterior colpotomy without difficulty.

Surgeons were aware of the merits of posterior colpotomy during the nineteenth century and many became remarkably adept in operating through the vagina. By 1900 Howard Kelly[4] had successfully performed 10 operations for tubal pregnancy through the vagina. In subsequent years several other surgeons, notably Babcock,[5] have reported their experiences with colpotomy for the diagnosis and treatment of a variety of lesions. More recently, Allen[6] has advocated this procedure before undertaking vaginal hysterectomy. We are convinced that posterior colpotomy provides a safe, accurate, and relatively easy approach to the diagnosis and treatment of pelvic disease in selected patients. The material presented in this paper summarizes the experience with this operation in the Temple University Hospital.

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Material

In recent years the posterior cul-de-sac has been punctured or opened, either for diagnosis or treatment, in 320 cases, or 2.6 per cent of the women admitted to the Gynecologic Division of the Department of Obstetrics and Gynecology during the period from March 1, 1948, to March 1, 1954. Posterior colpotomy was performed 231 times, colpocentesis 191 times, and culdoscopy but 17 times. Most of the procedures were performed by residents. Diagnostic colpocentesis was frequently performed just before the cul-de-sac was opened; if needle aspiration was inconclusive, the posterior fornix was usually incised, but in many of the patients with ruptured tubal pregnancy, abdominal laparotomy, rather than colpotomy, was selected, if a large amount of blood was withdrawn through the needle. The majority of the 320 were Negro ward patients; 27 per cent were nulliparous; the youngest was 16 years of age and the oldest 63.

Indications

The indications for the procedures are listed in Table I. All three of the procedures serve a more useful purpose in the diagnosis of pelvic disease than in its treatment. In 11 instances the cul-de-sac was opened for the purpose of performing an operative procedure rather than to examine organs. Nineteen of the ectopic pregnancies diagnosed by posterior colpotomy were removed through the vagina.

TABLE I. INDICATIONS FOR CUL-DE-SAC EXPLORATION

INDICATIONS	NO. PATIENTS	COLPOTOMY	COLPOCENTESIS	CULDOSCOPY	COMBINATION
Diagnostic.—					
Suspected ectopic pregnancy	209	129	171	12	103
Suspected pelvic inflammatory disease	45	42	10	0	7
Pedunculated pelvic mass	42	37	7	2	8
Hematoma	4	3	2	0	1
Pelvic pain	6	6	1	3	0
Infertility	3	3	0	0	0
	309	220	191	17	119
Surgical.—					
Tubal ligation	2	2	0	0	0
Bilateral oophorectomy	2	2	0	0	0
Biopsy of pelvic mass	5	5	0	0	0
Removal of prolapsed tube	1	1	0	0	0
Removal of foreign body	1	1	0	0	0
	11	11	0	0	0
Total	320	231	191	17	119

Technique for Colpocentesis and Colpotomy

All the procedures reported here were performed in the operating room with the patient anesthetized, prepared with Septisol, and draped. Most were operated upon in the lithotomy position with the buttocks elevated above the head but colpotomy has also been performed in the inverted jackknife position.

After preliminary bimanual examination, the rectum and posterior vaginal wall are depressed with a weighted speculum, or a right-angle retractor, and the posterior lip of the cervix is grasped with a tenaculum and pulled downward and anteriorly toward the pubis, thereby exposing the posterior vaginal fornix. For colpocentesis, a long 12 to 15 gauge short-beveled needle, attached to a 20 c.c. syringe, is thrust through the vaginal mucosa and the peritoneum in the midline, about 2 cm. posterior to the point at which the vaginal mucosa becomes adherent to the cervix. The course of the needle is parallel to the posterior wall of the uterus. The plunger of the syringe is withdrawn after the wall is penetrated. If nothing is aspirated, the needle is pulled back slightly and then is reinserted more deeply at a different angle. If blood is obtained, the needle tip is advanced, and aspiration is repeated to make certain that it is in the blood-filled cul-de-sac rather than in a blood vessel.

For posterior colpotomy, the vaginal mucosa and the underlying peritoneum are seized with two Allis forceps and a transverse incision is made between them in the raised fold of tissue about 2 to 3 cm. from the cervix. An attempt is made to incise both the vagina and the peritoneum together, rather than separately, to reduce bleeding. After the initial incision is made, the peritoneum and the vaginal mucosa are united with a single suture anteriorly, and another posteriorly, the ends being left long for traction. The incisions are then extended far enough laterally to permit palpation and inspection of the pelvic structures. Sutures are placed at each angle to reduce bleeding. Whenever it is necessary to obtain additional exposure, the incision is extended beyond the uterosacral ligaments which are clamped close to their uterine attachments to avoid injuring the ureters, and are then cut and ligated. The organs are exposed with two Heaney retractors, the bowel is packed away with gauze, and the oviducts and the ovaries are brought into view with Babcock visceral forceps. Exposure of the adnexa can often be facilitated by rotating the uterus posteriorly with an intrauterine sound. This is usually preferable to tension on the posterior wall with a tenaculum or a similar toothed instrument, because it does not produce bleeding. At the completion of the operation or examination, the incision is closed with a single layer of chromic catgut sutures which penetrate both the peritoneum and the vaginal wall. Each uterosacral ligament should be reattached to the uterus with a single suture.

As Decker[7] has pointed out, the apex of the cul-de-sac is widened, and the bowel is displaced upward when the patient is in the knee-chest position. Because of this, we have also performed posterior colpotomy in the inverted jackknife position. This provides a better view of the posterior wall of the uterus and of the tubes. In a review of the literature, we have found no reference to the performance of colpotomy in this manner.

Results

Colpocenteses.—Of the 191 colpocenteses performed, the result was inaccurate in 36, or 19 per cent, and in another 19, or 10 per cent, the procedure was inadequate for establishing the correct diagnosis. In 10 cases of ruptured ectopic pregnancy, the cul-de-sac tap was negative, even though there was free blood present within the peritoneal cavity. In 6 women with normal pregnancy, suspected of having tubal gestation, blood was aspirated. Blood was also aspirated in 3 who were having abortions, 4 with corpus luteum cysts, 1 with appendicitis, 2 with acute salpingitis, as well as in 3 with normal pelvic findings (Table II).

TABLE II. ANALYSIS OF COLPOCENTESES

DISEASE	NO.	FALSE POSITIVE	FALSE NEGATIVE	% FAILURE
Ectopic pregnancy	131	7	10	12
Normal pregnancy	10	6	0	60
Abortions	12	3	0	25
Appendicitis	1	1	0	100
Corpus luteum cyst	9	4	0	44
Salpingitis	10	2	0	20
Normal pelvis	18	3	0	17
Total	191	26	10	18

Colpotomy.—It was possible to make a correct diagnosis in all but 5 cases after posterior colpotomy had been performed. In these 5 patients the diagnosis was incomplete. In each one, tubal pregnancy was strongly suspected because of a blood-filled cul-de-sac, but it was impossible to expose the tubes adequately because of old inflammatory changes; consequently laparotomy was resorted to.

Colpocentesis and colpotomy are compared in Table III in regard to diagnostic accuracy.

TABLE III. COMPARISON OF COLPOCENTESIS AND COLPOTOMY AS TO RELIABILITY

ITEM	COLPOCENTESIS	COLPOTOMY
Number	191	231
Incomplete diagnoses	19	5
Inaccurate diagnoses	36	0
Error of complete and accurate diagnoses	28.8%	2.1%

Complications.—Complications developed in 28 of the 231 patients, or 12 per cent, upon whom colpotomy was performed. Fifteen had febrile courses due to (a) exacerbation of pelvic inflammatory disease (7 cases), (b) urinary tract infection (5 cases), (c) infected hematoma in the incision (1 case), and (d) pelvic cellulitis (2 cases). The latter remained in the hospital for 28 and 30 days. The incidence of febrile morbidity following colpotomy was 6.5 per cent.

Four patients had abortions after colpotomy, but each was bleeding and the abortion was already in progress when the patient was operated upon. Colpotomy was performed in 28 other pregnant women without incident.

Four patients bled as a result of the manipulations necessary to expose the diseased tissue. In one the broad ligament was lacerated by a retractor, and the other 3, in whom the bleeding occurred during attempts to expose the tubes, had severe chronic pelvic inflammatory disease. Laparotomy was necessary in all 4 to control the bleeding.

In 3 patients, the rectosigmoid, which was adherent to the posterior uterine wall, was opened. The perforations were sutured and healed without incident.

Two patients complained of dyspareunia after posterior colpotomy. In one with an indurated, tender scar the incision had probably been made too close to the cervix. In the other, the cul-de-sac seemed normal to palpation. This patient also was frigid and had other emotional problems and the pelvic symptoms were thought to be of psychogenic origin.

Length of Hospitalization.—When colpotomy was performed as a diagnostic procedure, the average period of hospitalization after the operation was

3.5 days. When a definitive surgical procedure was done through the posterior cul-de-sac, the period of hospitalization was 5.6 days. In abdominal laparotomy for diagnosis, the average hospitalization was 5.8 days, while in salpingectomy, oophorectomy, or similar procedures it was 8.1 days.

Comment

Unless the patients are carefully selected for colpotomy, and unless it is performed properly, the incidence of complications will be high. Exploration through the vagina should not be done in any patient suspected of having appendicitis or any other bowel or upper abdominal lesion, because it is impossible to expose and inspect structures other than those in the pelvis. The cul-de-sac must be free and pliable; consequently patients in whom the rectosigmoid may be adherent to the uterus because of endometriosis or infection, those in whom there may be multiple pelvic adhesions from inflammatory disease or previous operative procedures, and those with fixed pelvic masses should be operated upon by some other approach. In this series, 19 of the 28 patients in whom complications developed had chronic pelvic infection.

The position in which the patient is placed for the operation may vary depending upon the tentative diagnosis. If an abdominal laparotomy may be necessary to correct the disease, for instance, in suspected tubal pregnancy with moderate bleeding, the diagnostic colpotomy should be performed in the exaggerated lithotomy position. For tubal procedures, oophorectomy, ovarian biopsy, and similar procedures, or for the study of pelvic pain or adnexal masses, the patient may be placed in the inverted jackknife position because it provides somewhat better exposure. Patients suspected of having intraperitoneal bleeding probably should not be operated upon in this position, even though it seems likely that vaginal salpingectomy can be performed, because considerable delay and manipulation are necessary to change to the dorsal position on the table, if the required operation cannot be completed through the vagina.

A common cause of excessive bleeding and subsequent induration and pain in the incision is the blunt separation of the vagina from the peritoneum as the cul-de-sac is being opened. It is far easier to open and close the incision, and to control bleeding, if a clean incision is made through the entire thickness of the free portion of the posterior fornix. If the incision is made too close to the cervix it is impossible to avoid splitting the layers and at times the cervix or the posterior uterine wall itself may be cut.

Adequacy of exposure is essential. This can be obtained in part by position and by packing off the bowel, but the size of the incision is of far greater importance. If the fornix is wide and the incision is placed properly, there usually is enough room between the uterosacral ligaments for diagnostic colpotomy, but one should never hesitate to cut these structures if additional exposure is required to carry out the necessary manipulations.

Summary

Posterior colpotomy is a far more accurate method for diagnosis of pelvic disease than is colpocentesis, and the technique is easier to learn than is that for culdoscopy. The length of hospitalization is short, the discomfort is slight, and the complications are few. Its main uses are in the differential diagnosis and, at times, treatment of ectopic pregnancy, the evaluation of enlargements of the adnexa, the study of endocrine and infertility problems, the evaluation of patients with unexplained pelvic pain, and for certain operative procedures

such as salpingectomy and oophorectomy. The main contraindications to the procedure are pelvic infection, endometriosis, pelvic adhesions, and the possibility that the symptoms may arise outside the pelvis.

References

1. Decker, Albert: Am. J. Surg. **73**: 313, 1947.
2. Doyle, Joseph B.: New England J. Med. **244**: 930, 1951.
3. Bradbury, William C.: West. J. Surg. **60**: 377, 1952.
4. Kelly, Howard A.: Johns Hopkins Hosp. Bull. **7**: 209, 1896.
5. Babcock, W. Wayne: AM. J. OBST. & GYNEC. **17**: 53, 1929.
6. Allen, Edward: S. Clin. North America **33**: 193, 1953.
7. Decker, Albert: Culdoscopy, Philadelphia, 1952, W. B. Saunders Company.

A SIMPLIFIED STAINING TECHNIQUE FOR THE STUDY OF CHROMOSOMAL SEX IN ORAL MUCOSAL AND PERIPHERAL BLOOD SMEARS*

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THE determination of chromosomal sex in patients with endocrine disorders has become an increasingly important diagnostic aid. Chromosomal sex determination in the human dates back to the work of Moore and Barr[1] in 1953 when they demonstrated the presence of a dense pyknotic area in the nucleus of the cell which was characteristic in the female. They postulated that this was due to a fusion of the heterochromatic portions of the XX chromosomes of the female cells. Since the XY chromosomes of the male seemingly fail to form a chromatin mass of comparable size, this mass has been used to distinguish between the genetic male and the genetic female. For this reason it has been referred to as the "sex chromatin." This phenomenon has been demonstrated in human skin biopsies[2] and in buccal[3, 4] and vaginal[5] smears (Fig. 1). It has also been reported that fetal sex may be predicted during pregnancy by the observation of cells from the amniotic fluid for the presence or absence of this sex chromatin.[6]

In recent studies on human blood smears, Davidson and Smith[7] reported the observation of a "drumstick-like" mass projecting from the nucleus of the mature neutrophilic leukocyte of the female (Fig. 2). Since projections of this size and shape are nearly always absent in male smears, they concluded that this "drumstick" was the female sex chromatin in the blood cells. It was their further belief, based on numerous observations, that the XY chromosomes of the male produced smaller clublike or nodular projections from the nucleus (Figs. 3 and 4). These may, however, with a modicum of experience, be distinguished easily from the "drumstick."

Sun and Rakoff[8] conducted a study to evaluate the usefulness of the blood smear as a diagnostic test for genetic sex determination which confirmed the initial observations of Davidson and Smith. The Rakoff group utilized the May-Grünwald-Giemsa technique and the Feulgen methods of staining. Other groups have reported similar studies using the Wright stain technique.[9]

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The purpose of this present study was to develop a staining technique[10, 11, 12] which would combine simplicity with a high percentage of accuracy, and to compare the accuracy of the oral mucosal smear and the peripheral blood smear in the detection of chromosomal sex in the human being. The problems that had to be overcome included discoloration by staining too thick a smear, and the interference produced by toxic granulation and/or other distracting artifacts, with the attempt at the same time to increase the prominence of the stained nucleus of both the leucocyte and the epithelial cell from the buccal mucosa. Slides which stained poorly or contained too little material were discarded and not included in this series.

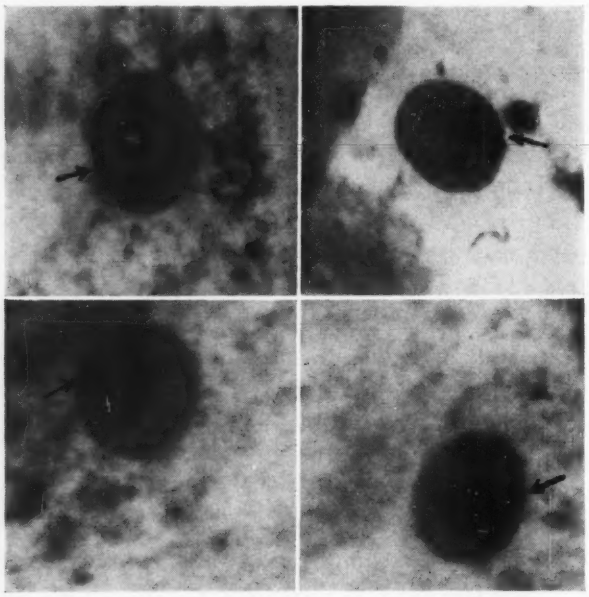

Fig. 1.—Arrows point to sex chromatin in oral mucosal smears.

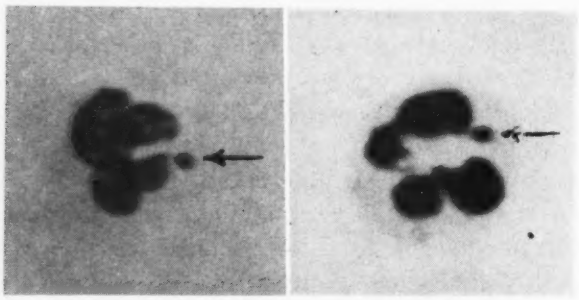

Fig. 2.—Typical "drumstick" chromatin mass in leukocytes.

Material and Technique

Blood Smears.—A peripheral blood smear of even distribution was used. When the slides were completely dry they were fixed in absolute methyl alcohol for 1 or 2 minutes and then subjected to the following procedure:

1. Stain with 0.5 per cent pinacyanole* in 70 per cent methanol—30 seconds.

*Obtainable from the Eastman Kodak Company, Rochester, N. Y., or from Southeastern Biochemicals, Box 53, Augusta, Ga.

2. Dilute with Wright's buffer solution, pH 6.4—30 seconds.
3. Wash under running tap water.
4. Decolorize with 50, 70, 95 per cent, and absolute alcohol—30 seconds.
5. Air dry and read under oil immersion.

Oral Mucosal and Vaginal Smears.—Material for the oral mucosal smear was obtained by vigorously scraping the inner surface of the cheek with the edge of a tongue depressor and spreading the material on a glass slide.

The vaginal smear may be obtained by swabbing the vaginal canal with a cotton applicator and rolling the material onto a clean slide.

The slides were immediately fixed by immersion in an alcohol-ether mixture (equal parts) for 2 to 24 hours. They were then subjected to the following procedure:

1. Stain with 0.5 per cent pinacyanole in 70 per cent methanol—45 seconds.
2. Dilute with Wright's buffer solution, pH 6.4—45 seconds.

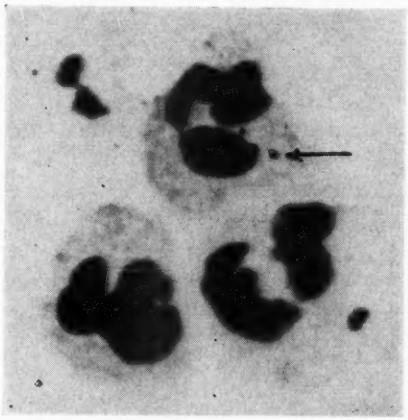

Fig. 3.—Arrow points to small and faintly staining clublike structures which may be found in male and female patients, and is not to be confused with typical "drumsticks."

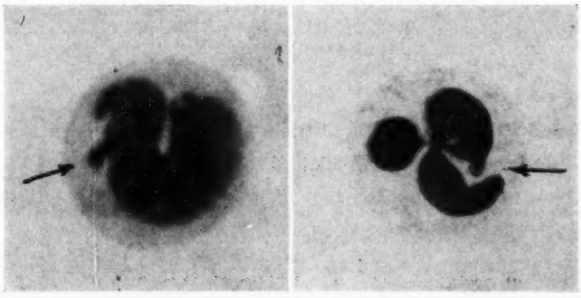

Fig. 4.—Sessile nodules found in male and female cases and not to be confused with "drumstick" chromatin mass.

3. Wash under running tap water.
4. Decolorize with 50, 70, and 95 per cent (one minute in each), and absolute alcohol—30 seconds.
5. Clear in xylene twice.
6. Mount in balsam.

Method of Study

The purpose of the first part of the study was to familiarize the investigator with the technique of preparing the smears for study of sex differentiation and with interpretation of findings.

Table I is presented to show the results of 80 slides (on 20 subjects), 40 oral mucosal smears and 40 blood smears, studied by the interpreter, who knew the sex of the donor.

TABLE I. KNOWN SLIDES OF KNOWN NORMAL PATIENTS

SMEARS	MALE	FEMALE	TOTAL PATIENTS	TOTAL SLIDES	NO. ERRORS	NO. CORRECT	% ERROR	% CORRECT
Oral mucosa	8	12	20	40	0	40	0	100
Blood	8	12	20	40	0	40	0	100

The next step was the study of 30 patients with known endocrinopathies and other medical disorders (Table II).

TABLE II. PATIENTS WITH KNOWN ENDOCRINOPATHIES AND OTHER MEDICAL DISORDERS

SMEARS	MALE	FEMALE	TOTAL PATIENTS	TOTAL SLIDES	NO. ERRORS	NO. CORRECT	% ERROR	% CORRECT
Oral mucosa	10	20	30	60	0	60	0	100
Blood	10	20	30	60	0	60	0	100

The third and most important part of the present study dealt with 140 unknown slides of known normal patients. In this case all the slides were arbitrarily numbered to conceal identity; sometimes one patient had slides taken more than once (Table III).

TABLE III. UNKNOWN SLIDES OF KNOWN NORMAL PATIENTS

SMEARS	MALE	FEMALE	TOTAL PATIENTS	TOTAL SLIDES	NO. ERRORS	NO. CORRECT	% ERROR	% CORRECT
Oral mucosa	19	21	40	70	0	70	0	100
Blood	19	19	38	70	2*	68	02.85	97.14

*One 24-year-old male and one 52-year-old female were diagnosed incorrectly on one slide and correctly on another.

Twelve patients with sexual abnormalities were added to this study (Table IV).

TABLE IV. PATIENTS WITH SEXUAL ABNORMALITIES—12 CASES

DIAGNOSIS	ORAL SMEAR	BLOOD SMEAR
Female pseudohermaphroditism	Female	Female
Male pseudohermaphroditism	Male	Male
Male pseudohermaphroditism	Male	Male
Hypogonadism	Male	Male
Hypogonadism	Male	Male
Hypogonadism	Male	Male
Hirsutism, enlarged clitoris	Female	Female
Gonadal dysgenesis	Male	Female
Gonadal dysgenesis	Male	Female
Gonadal dysgenesis	Male	Female
Congenital absence of vagina	Female	Female
Congenital absence of uterus	Female	Female

In the oral mucosal smears, it was necessary to find 6 cells in a total count of no more than 100 cells with the "sex chromatin" (Fig. 1) to make a diagnosis of female sex pattern. When less than 4 cells per 100 containing "sex chromatin" were found, the patient was considered a male. There is very little difficulty in interpretation of smears of the oral mucosa, and proficiency in reading them is soon acquired.

The blood smears were more difficult to interpret and more time was required to study them. A total of 500 cells or less may be counted, and it is necessary to find 6 "drumsticks" (Fig. 2) for the diagnosis of female pattern. It is essential to have a well-prepared slide with proper staining.

Results

Of the 80 smears obtained from the known normal patients the readings were correct in 100 per cent of the cases (Table I).

In the patients with known endocrine disturbances and/or medical disorders, the readings were correct in all cases (Table II).

In the group of unknown normal subjects the percentage of correct diagnosis from the oral mucosal smears was 100 per cent from the blood smears, 97.14 per cent (error = 2.85 per cent). Of the 2 slides which were misinterpreted, one patient was a male and the other a female. Study of a second smear from these particular patients yielded the correct interpretation.

In 9 of the 12 in the group with sexual abnormalities the oral and blood smears yielded identical results. In 3 cases of gonadal dysgenesis, however, the oral mucosal smear was interpreted in each instance as being male, while the blood smear was interpreted as being female.

Comment

The results reported in this paper show clearly that the simplified technique for the determination of chromosomal sex in peripheral blood, and in oral mucosal smears is an easy, quick method with a high percentage of accuracy. The mucosal smears proved 100 per cent accurate and the blood smears 97.14 per cent accurate in the series wherein normal patients were studied. It is necessary to point out, however, that the reliability of the method is dependent upon using technical precaution and obtaining sufficient material on the slides.

A discrepancy between oral and blood smears was found in 3 cases of gonadal dysgenesis. In a previous unpublished study a dissociation between the blood and mucosal smears was also found in one case of Klinefelter's syndrome. The significance of this observation is not clear at the present. Furthermore, a tall eunuchoid female with dysgenetic gonads was studied and reported as having definite female sex chromatin patterns.[13] The skin biopsies and the oral and vaginal mucosal smears were seen by several prominent investigators who corroborated the diagnosis of female chromatin patterns. At a later date blood smears were obtained and to our surprise repeated studies revealed only 3 to 4 typical "drumsticks" in 500 cells counted. The blood smears were sent to G. I. M. Swyer[14] of London, England, who corroborated this finding. We now have encountered this dissociation in 5 instances. The full significance of the sex chromatin pattern in gonadal dysgenesis and in Klinefelter's syndrome has not as yet crystallized.[15, 16, 17]

Summary

Oral mucosal and blood smears were studied in 90 sexually normal patients of both sexes, and in 12 patients with sexual abnormalities. In the normal cases the diagnosis was correct in 100 per cent of the oral mucosal smears and 97.14 per cent of the blood smears. In the abnormal group, there were 3 cases of gonadal dysgenesis in which the diagnosis was different in the blood and mucosal smears. Thirty patients with known endocrinopathies and other medical disorders were tested and the diagnosis was correct in 100 per cent of the cases. In our over-all studies to date 5 cases have been encountered in which there was a discrepancy between mucosal and blood smears.

Conclusions

1. A new and simplified technique is described with the use of pinacyanole as the stain.

2. The method proved to be moderately easy and quick with a high percentage of accuracy.

3. Proficiency in preparing and reading the slides may be obtained in a relatively short time.

4. It is felt that the mucosal smears gave a more accurate index of chromosomal sex than did the blood smears.

Addendum.—Since this paper was submitted for publication, an article has appeared which helps to explain the variance in the results obtained in our mucosal and blood smear study of sex chromatin patterns. The article by Ashley[18] concludes that the satellite body of Davidson and Smith is not identical with the heterochromatin mass and must be regarded as a sex characteristic rather than as the XX complex.

References

1. Moore, K. L., and Barr, M. L.: Acta anat. **21**: 197, 1954.
2. Marberger, E., and Nelson, W. D.: Anat. Rec. **118**: 399, 1954.
3. Moore, K. L., and Barr, M. L.: Lancet **2**: 57, 1955.
4. Greenblatt, R. B., deAcosta, O. M., Vazquez, E., and Mullins, D. F.: J. A. M. A. **161**: 683, 1956.
5. Carpenter, P. L., Stotle, L. A. M., and Visschers, G. P.: J. Clin. Endocrinol. **16**: 1, 1956.
6. Serr, D. M., Sachs, L., and Danon, M.: Bull. Research Council of Israel **5B**: 137, 1955.
7. Davidson, W. M., and Smith, D. R.: Brit. M. J. **2**: 6, 1954.
8. Sun, L. C., and Rakoff, A. E.: J. Clin. Endocrinol. **16**: 1, 1956.
9. Briggs, D. K., and Kupperman, H. S.: J. Clin. Endocrinol. **16**: 1163, 1956.
10. Greenblatt, R. B.: A New Simplified Staining Procedure for Oral Mucosal Smears in Determination of Chromosomal Sex, Abstracts, The Endocrine Society, 38th Meeting June 7-9, 1956, p. 75.
11. Greenblatt, R. B., Dienst, R. B., and West, R. M.: Am. J. Syph., Gonorr., & Ven. Dis. **35**: 291, 1951.
12. Greenblatt, R. B.: J. M. A. Georgia **38**: 95, 1949.
13. Greenblatt, R. B., Carmona, N., and Higdon, L.: J. Clin. Endocrinol. **16**: 235, 1956.
14. Swyer, G. I. M.: Personal communication.
15. Bunge, R. G., and Bradbury, J. T.: J. Clin. Endocrinol. **16**: 1117, 1956.
16. Grumbach, M. M., Van Wyk, J. J., and Wilkins, L.: J. Clin. Endocrinol. **15**: 1161, 1955.
17. Bradbury, J. T., Bunge, R. G., and Boccabella, R. A.: J. Clin. Endocrinol. **16**: 689, 1956.
18. Ashley, D. J. B.: Nature **179**: 969, 1957.

EXPERIMENTAL AND CLINICAL STUDIES ON A NEW SYNTHETIC ESTROGEN, AN ALLENOLIC ACID DERIVATIVE, VALLESTRIL

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SECTION I. EXPERIMENTAL STUDIES ON THE ESTROGENIC ACTIVITY OF VALLESTRIL

IN GENERAL, there are few chemical structural characteristics of substances with estrogenic activities, and it has been widely known that even substances with other than steroid structure have marked estrogenic activity and produce physiologic effects similar to those of the natural estrogens.[1] These substances, for clinical use, should show remarkable estrogenic activity without side effects.

Studies on the chemistry of stilbene derivatives by Dodds and associates[5] in 1938 have been monumental in the field of synthetic chemistry, and it was highlighted by the synthesis of marrianolic acid, doisynolic acid and derivatives of each, followed by that of estrone.[22-26]

Following this, in 1947-1948, Courrier, Horeau and Jacques[2, 3, 4] were able to synthesize allenolic acid, a naphthalene compound derivative, which was studied in detail by Julia.[8] The present report deals with the experimental results of work with 3-(6-methoxy-2-naphthyl)-2-2-dimethyl pentanoic acid, a derivative of allenolic acid, manufactured under the trade name Vallestril.

Chemical Structure of Allenolic Acid Derivate and Its Estrogenic Activity

As seen in Fig. 1, marrianolic acid (*2*) and doisynolic acid (*3*) were obtained from estrone (*1*), while bisdehydrodoisynolic acid (*5*) was synthesized from equilenin (*4*), by opening the D-ring of the natural steroid. Subsequently, Horeau and Jacques, by opening, in addition, the C-ring created allenolic acid, so named after Allen. These substances with basically simplified chemical structures show marked estrogenic activity.

From the studies of Courrier and Miescher and others on substances (*9*) and (*10*) the COOH group appeared all important for the physiologic effects of allenolic acid and its derivatives; when the OH group was removed it was noted that in the case of substance (*8*) the potency was reduced to one-tenth that of the methoxy compound.[7, 8]

Similarly, when the OH group is removed, the effective potency in comparison of bisdehydrodoisynolic acid is reduced to one-fiftieth and of stilbestrol to one-fourth. Judging from the fact that the hydroxidation in vivo can be

more readily achieved with stilbestrol than with allenolic acid, and with most difficulty with bisdehydrodoisynolic acid, the difference in decrease in the physiologic effects of each compound, due to the removal of the OH group stated previously, may presumably be due to such difference in the extent of the dehydroxidation in vivo, resulting in substances with more profound physiologic effects, as has been pointed out by Julia.[8]

Meanwhile, the naphthalene group raises a problem other than the combination or removal of the effective group mentioned above, namely, notwithstanding that physiologically estrone is thirty to forty times as potent as equilenin, doisynolic acid made from estrone is less potent than bisdehydrodoisynolic acid produced from the latter. In other words, absence of a double bond in the B-ring of the steroid nucleus results in a more potent compound, whereas opening of the D-ring with absence of the double bond in the B-ring results in a less potent compound. According to Wieland and Miescher,[37] allenolic acid derivative also is more potent than that saturated in the B-ring (*9*), and saturation of the A-ring results in marked reduction in physiologic potency of estrone, estradiol,[30, 31, 32] and also allenolic acid derivatives.[8]

Experimental Methods

1. Preparation of Experimental Materials.—A white tablet weighing approximately 0.3 Gm. and containing 3 mg. of Vallestril, and a peanut oil solution containing 10 mg. of Vallestril per cubic centimeter were employed. Prior to use, the tablets were pulverized in a mortar and pestle in water and then made into an emulsion by the addition of carboxymethylcellulose or lactose. The oil preparation was then made to desired dilution by the addition of peanut oil. Vallestril was compared with peanut oil solutions of estrone, estradiol benzoate, estradiol-17-valerianate, diethylstilbestrol, ethinyl estradiol (Schering), Euvestin (Takeda), and Robal (Chugai), each containing 0.05 mg. of active principle. Each was diluted and prepared exactly as was Vallestril.

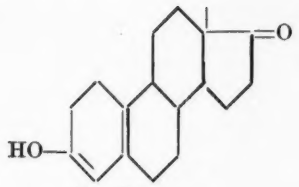
2. Experimental Animals, Methods of Administration and Examination of Vaginal Smears.—

(1) Experimental animals: Spayed mature rats and mice, the castration of which had been performed via a dorsal approach, were employed. Only animals still in anestrus three weeks after operation were employed in the experiment. Animal weight ranges were 120 to 150 grams for rats and 12 to 15 grams for mice. Five animals formed one group for each section of the experiment.

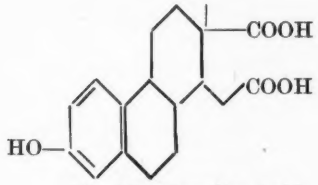
(2) Methods of administration: Two-tenths cubic centimeters of the oil solution was injected into the dorsal subcutaneous tissues of each rat, and 0.1 c.c. into each mouse. Oral administration was achieved by securing the animal, fasted for one day, in the dorsosupine position, inserting a Nélaton catheter into the animal's stomach, and administering the desired measured dose (1 to 2 c.c. for each rat and 0.2 c.c. for each mouse), following which the catheter was cleared in situ with an equal volume of normal saline.

Application to selected skin surfaces by inunction technique was carried out with the use of an ointment produced by mixing the test preparation thoroughly in a heated fluid polyethyleneglycol base which was then cooled to a creamy state, then applied to a shaved area, 2.0 by 2.5 cm., on the dorsal surface of each animal. The test volume of ointment was 0.2 Gm.

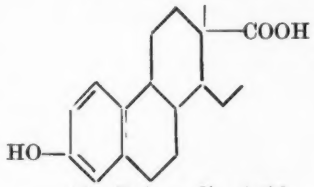
(3) Examination of vaginal smears: Twenty-four hours after administration of the test material, twice daily, vaginal smears were obtained by means



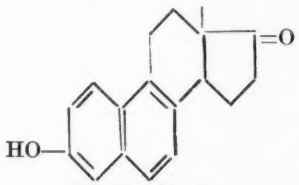
(1) Estrone



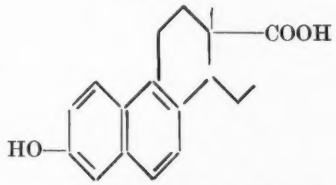
(2) Marrianolic Acid



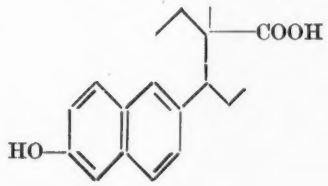
(3) Doisynolic Acid



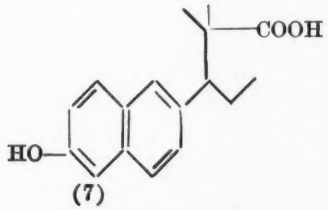
(4) Equilenin



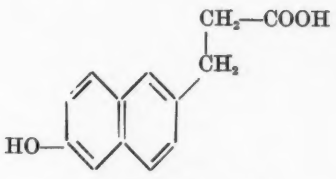
(5) Bisdehydrodoisynolic Acid



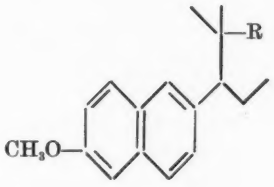
(6)



(7)

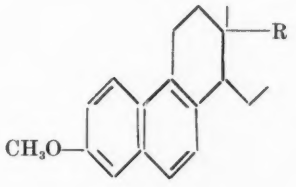


(8) Allenolic Acid



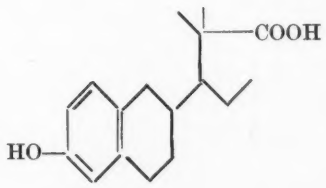
(9)

Minimum dose to produce estrus
R=COOH 1.5 γ (Courrier)
R=CH_3 100 γ (Courrier)



(10)

Minimum dose to produce estrus
R=COOH 0.1-0.2 γ (Miescher)
R=CH_3 5-20 γ (Miescher)
R=C_2H_5 1000 γ (Miescher)



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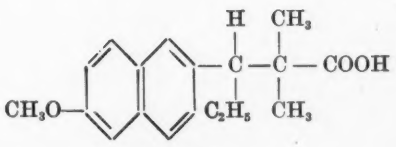

(12) Vallestril

Fig. 1 —Formulas of substances with estrogenic activity.

of a sterile platinum loop. Estrogenic effect was based on the appearance of completely nonnucleated cornified cells in accordance with the Allen-Doisy test. Comparison was made on results in groups of 5 test animals.

3. Method of Administration to Castrated Women.—One tablet of Vallestril (3 mg.) was administered to a woman who had at least six months previously undergone panhysterosalpingo-oophorectomy for carcinoma of the cervix and whose postoperative course had been uneventful. Following oral ingestion of Vallestril, blood was drawn from the cubital vein after 3, 6, 12, and 24 hour periods and estimation of estrogen titer was carried out by the method of Kobayashi and Nakayama.[9]

Experimental Results

1. Estrogenic Activity of Vallestril in Case of Subcutaneous Injection.—

(1) Minimum dose to produce estrus in spayed mature rats: As shown in Table I, the minimum dose of Vallestril to produce estrus is 1 γ. Estrone and diethylstilbestrol in comparison are twice and four times as potent, respectively.

TABLE I. AMOUNT OF SUBCUTANEOUS VALLESTRIL REQUIRED TO PRODUCE ESTRUS IN MATURE SPAYED RATS

ESTROGEN	DOSE OF INJECTION (0.2 C.C.) (γ)	INCIDENCE OF ESTRUS (%)
Estrone	0.50	60
Diethylstilbestrol	0.25	60
Vallestril	2.0	100
	1.0	60
	0.5	0
	0.02	0

(2) Minimum dose to produce estrus in spayed mature mice: As shown in Table II, the minimum dose to produce estrus is 0.4 γ, this potency corresponding to less than ¼ that of estrone, 1/16 that of estradiol benzoate, less than 1/20 that of estradiol-17-valerianate, and ¼ that of diethylstilbestrol.

TABLE II. AMOUNT OF SUBCUTANEOUS VALLESTRIL REQUIRED TO PRODUCE ESTRUS IN MATURE SPAYED MICE

ESTROGEN	DOSE OF INJECTION (0.1 C.C.) (γ)	INCIDENCE OF ESTRUS (%)
Estrone	0.10	100
Estradiol benzoate	0.02	40
	0.025	100
Estradiol-17-valerianate	0.02	80
	0.025	100
	0.05	100
Diethylstilbestrol	0.05	40
	0.1	80
Vallestril	0.3	40
	0.4	80

TABLE III. AMOUNT OF ORAL VALLESTRIL REQUIRED TO PRODUCE ESTRUS IN MATURE SPAYED RATS

VALLESTRIL (DOSAGE IN γ)	VOLUME OF FLUID (C.C.)	INCIDENCE OF ESTRUS (%)
50	2.0	100
30	1.2	100
10	2.0	100
5	1.0	100
4	2.0	60
2	1.0	0

2. Estrogenic Activity of Vallestril in Case of Oral Administration.—

(1) Minimum dose to produce estrus in spayed mature rats: As shown in Table III, the minimum dose of Vallestril necessary to produce estrus is 4 γ. Dosage over 5 γ results in a 100 per cent incidence of estrus, 4 γ results in 60 per cent showing estrus and 2 γ produces estrus in none. This indicates that the minimum dose for estrus by oral administration is four times that of a single injection of oil solution (1 γ).

(2) Minimum dose to produce estrus in spayed mature mice: In spayed mature mice, Vallestril in dosage of 1 γ given in 0.4 c.c. produced estrus in 4 out of 5 animals (80 per cent). By comparison, the subcutaneous injection of an oil solution is two and one-half times as effective as the oral route of administration in producing estrus; by injection, 0.3 γ will produce estrus in 40 per cent of animals while 0.4 γ will produce the desired results in 80 per cent.

(3) Maintenance of estrus in the spayed mature rat: As seen in Table IV, the minimum dose of Vallestril to produce estrus, namely, 4 γ, will maintain estrus for 1 to 2 days, 5 γ will effect estrus for 1 to 2 days, 10 γ for 2 to 3 days, and 30 γ for 4 to 10 days. Beyond the dosage of 30 γ estrus is prolonged only slightly. As much as 3,000 γ of Vallestril has been given as a single oral dose without significantly prolonging estrus. Fifty gamma of Robal, used in comparison, maintained estrus for a 10 to 11 day period. Follow-up examination of body weight and general condition of the test animals failed to disclose toxic abnormalities produced by the test material.

TABLE IV. DOSAGE OF VALLESTRIL AND ROBAL REQUIRED TO MAINTAIN ESTRUS IN MATURE RATS

ESTROGEN	DOSAGE IN γ	DAYS BEFORE APPEARANCE OF ESTRUS	NUMBER OF DAYS ESTRUS IS MAINTAINED
Vallestril	3,000	3	10-11
	50	3	7- 8
	30	3	4-10
	10	3	2- 3
	5	3	1- 2
	4	3	1-2 (only four)
	2	3	1 (only one)
Robal*	50	3	10-11

*Robal: 4,4-diacetoxy-diethylbibenzyl.

TABLE V. EFFECT OF ESTROGENS GIVEN CUTANEOUSLY ON MAINTENANCE OF ESTRUS

ESTROGEN	NUMBER OF ANIMALS	DOSE OF DRUG APPLIED (MG.)	VOLUME OF OINTMENT APPLIED (GM.)	DAYS ESTRUS MAINTAINED	DAYS BEFORE ESTRUS INDUCED
Vallestril	5	0.3	0.2	21.8	4
	5	0.001	0.2	2.8	4
Robal	5	0.001	0.2	2.0	4
Euvestin*	5	0.001	0.2	0.7	4
Contrast	5		0.2	0	0

*Euvestin: p,p'-dicarboethoxy-oxy-trans-α, β-diethyl stilbene.

3. Estrogenic Activity of Vallestril in Case of Dermal Application to the Spayed Mature Rat.—As shown ir Table V, percutaneous administration of 1 γ of Vallestril results in the maintenance of estrus in the test animal for an average of 2.8 days as compared to 2.0 days for Robal and 0.7 day for Euvestin; by dermal application of the Vallestril ointment, estrus was produced by approximately the minimum parenteral dose required to produce estrus.

Vallestril in dosage of 300 γ produced estrus for an average of 21.5 days; no estrogenic activity was noted if a polyethyleneglycol base was used. Topical application of Vallestril then has been shown to have effective absorption and prolonged action.

4. Blood Estrogen Levels Following Oral Estrogen Administration to Castrated Women.—Administration of 3 mg. of Vallestril to a castrated woman results in increased blood estrogen levels within 3 hours, with a maximum level after 12 hours, and rapid decline after 24 hours, as shown in Fig. 2. It is thought that daily oral administration of 3 mg. of Vallestril is sufficient to maintain a constant maximum blood level, because this level corresponds to that found at the peak of ovulation time in the normal menstrual cycle.[9] Clinical comparison of estrogen levels produced by oral administration of 3 mg. of Vallestril with those produced by Robal shows the latter to produce comparable titers when given in intramuscular doses of 2.5 mg.; 0.1 mg. of ethinyl estradiol by mouth showed but one-half the levels produced by 3 mg. of Vallestril given by mouth.

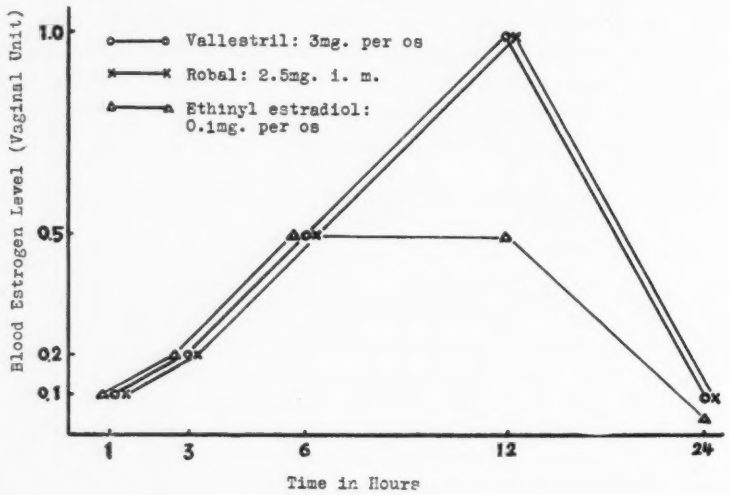

Fig. 2.—Composite graphs of blood estrogen levels following administration of different estrogens separately to 3 castrated women.

One vaginal unit is the biologic estrogenic activity produced by 0.001 γ of estrone benzoate administered via the castrated rat's vagina.

SECTION II. CLINICAL STUDIES WITH VALLESTRIL

Vallestril, which was synthesized as a naphthalene derivative of allenolic acid, has been studied experimentally and clinically principally in France and made its appearance side by side with other synthetic estrogens so far in use. Increased attention has been directed to Vallestril because of its clinical effectiveness and low incidence of deleterious side effects. As noted in the first section of this report, this preparation has been fully investigated in comparison with other synthetic estrogens and its physiologic effectiveness demonstrated by oral, subcutaneous, and percutaneous routes of administration. The present section reports results obtained with Vallestril in certain clinical problems peculiar to the field of obstetrics and gynecology.

Summary of References Concerning Clinical Results With Vallestril

Netter[28] reported on the effects of Vallestril on the endometrium and vaginal smears of castrated women, and Johnson[21] studied its ability to suppress lactation. Sturnick and Gargill[35] noted the salutary effectiveness without unpleasant side effects in the treatment of menopausal disorders; decreased urinary gonadotrophin excretion was noted without alteration of thyroid function as assessed by radioactive iodine balance studies; confirmation of the drug's effectiveness in the climacteric was made by Gennes, Bricaire, and Tubiana,[15] and metastatic lesions of prostatic malignancy by Gargill.[14] Influence of the drug on basal metabolism in the human female has been reported by Saito.[34] Other clinical observations have been made by Okuda and Kimura,[29] Izuchi and associates,[19] Narita and colleagues,[27] Sagawa and coworkers,[33] and ourselves.[13]

Experimental Methods and Materials

Patients studied in this series were selected from those attending the Obstetrical and Gynecological Department of the Tokyo University Hospital in the period from September, 1953, to December, 1954. Medication was usually given orally, but, on occasion, vaginal suppositories were employed. Clinical problems assessed included amenorrhea (29 cases), functional uterine bleeding (30 cases), inhibition of ovulation (2 cases), senile vaginitis (10 cases), prepubertal vulvovaginitis (7 cases), suppression of lactation (10 cases), and menopausal disorders (22 cases), making a total of 110 cases. Details of dose and route of administration of the drug are described in each category. As indicated, patients were investigated with regard to basal body temperature, endometrial biopsy (endometrium studied with hematoxylin-eosin stain), and examination of vaginal cytologic smears (Papanicolaou's method) and, at the same time, body weight, urinalysis (for albumin, sugar, urobilin, urobilinogen, and acetone), blood pressure, peripheral blood picture (Giemsa's stain), liver function tests, etc., were followed serially.

Experimental Results

1. Amenorrhea.—The range of the patients' ages was under 20 years in 2 cases, from 20 to 24 in 12 cases, 25 to 29 in 9 cases, and 30 to 36 in 6 cases, making a total of 29 cases. Amenorrhea had been present for less than 3 months in 14 cases, 4 to 6 months in 8 cases, 6 to 12 months in 3 cases, and longer than one year in 4 cases, including one case of primary amenorrhea. To these patients oral administration varying from 1 to 21 days was given, with total dosage ranging from 27 to 180 mg. Within two weeks following completion of therapy vaginal bleeding was noted in 20 of the 29 patients (69 per cent); included among the 9 patients without satisfactory clinical result were one with primary amenorrhea and one with amenorrhea for over two years. As shown by basal body temperature curve and histologic picture obtained by endometrial biopsy, this bleeding was "estrogen withdrawal" in type as expected following disappearance of estrogen support to the endometrium. Subsequent to "estrogen-withdrawal" bleeding, no true menstruation-like bleeding occurred.

Sturnick and Gargill[35] mentioned especially the difficulty in inducing vaginal bleeding when Vallestril is employed in the management of menopausal disorders. The above-mentioned incidence of vaginal bleeding was obtained in our series by the use of relatively large dosage schemes in a relatively short period of time. In comparison, the stilbene derivative, Euvestin, given orally in 0.5 mg. daily doses to a total dose of 10 mg., will effect vaginal bleeding

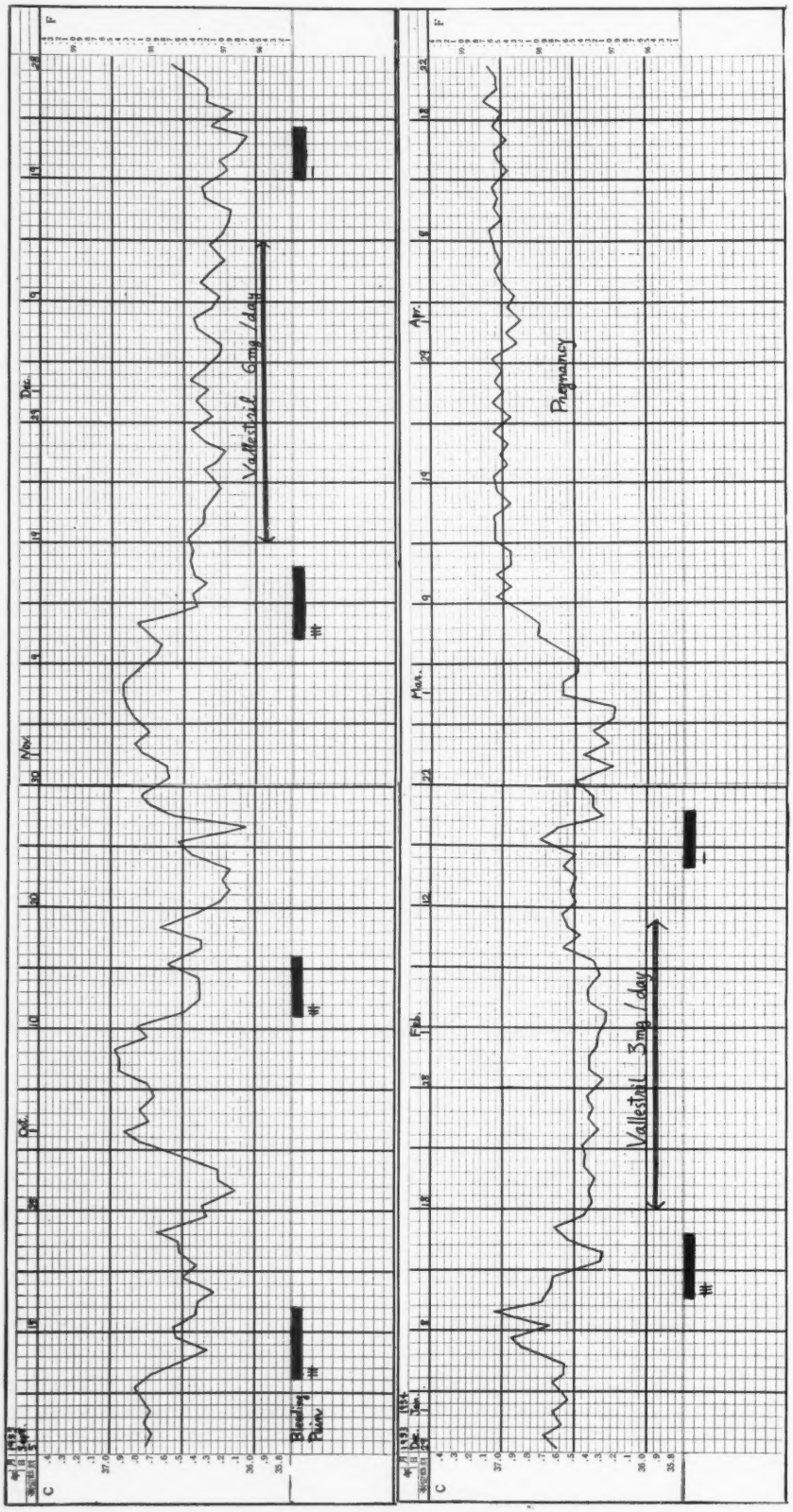

Fig. 3.—First case. Basal body temperature curve following oral administration of Vallestril to a 24-year-old woman with functional dysmenorrhea who subsequently became pregnant.

in case of amenorrhea only, while the bibenzyl derivative, Robal, achieved desired results in 16 of 17 cases when an average total oral dose of 11.8 mg. was administered. The histologic picture of the endometrium with these preparations will be reported separately.

2. Functional Uterine Bleeding.—Thirty patients, their ages ranging from 16 to 50 years and their parity from 0 to v, in whom functional bleeding had been present for less than one week in 9 cases, 2 to 3 weeks in 13 cases, 4 to 6 weeks in 6 cases, and 10 to 12 weeks in 2 cases, were assessed, in each of whom organic causes were ruled out by accepted clinical procedures including endometrial biopsy. Vallestril was administered orally in daily dosage of 3 to 18 mg. for periods ranging from 2 to 10 days and resulted in hemostasis in 22 cases (73.3 per cent). Bleeding ceased within 2 days in 13 cases (43.3 per cent), within 3 days in 17 cases (56.7 per cent), and within 5 days in 20 cases (66.7 per cent). An adequate dosage scheme is considered to be 6 to 9 mg. daily for a 3 to 5 day period.

As noted by Hamblen,[16] Fluhmann,[12] and others, functional uterine bleeding may occur from any histologic type of endometrium. In this series these findings were amply confirmed. Similarly, it was noted that uterine hemostasis was secured with an endometrium showing either a florid proliferative or secretory phase. The efficacy of Vallestril in achieving uterine hemostasis in functional uterine bleeding is noteworthy, and can be partially understood from assessment of the endometrial picture found at the termination of therapy. Cessation of therapy which had achieved hemostasis has, on occasion, been followed by recurrence of bleeding. While it is not clear whether or not this bleeding is secondary to cessation of Vallestril therapy, in most instances, hemostasis can be achieved once more by further administration of Vallestril.

3. Inhibition of Ovulation.—Inhibition of ovulation with the use of Vallestril was achieved in 2 unmarried girls aged 24 and 21, respectively, without any side effects. Basal body temperature curves of these patients are shown in Figs. 3 and 4. Dose and duration of therapy and duration of menstrual pain and bleeding are as shown in the figures. Both individuals showed no abnormalities on pelvic examination and were considered to have functional dysmenorrhea. Omitting details of subjective improvement, clinical results are summarized as follows:

(1) While they were ingesting 3 to 6 mg. of Vallestril daily, the basal body temperature curves, which previously had been biphasic, reverted to a monophasic type at a lower basal temperature and endometrial biopsy disclosed the absence of ovulation.

(2) The low temperature monophasic picture was maintained as long as administration was continued past the ovulation time for the individual menstrual cycle, and the endometrial picture at the onset of withdrawal bleeding following cessation of therapy was anovulatory in type.

(3) Several days after the blood estrogen levels decreased in accordance with the discontinuation of therapy, the basal body temperature rose and the endometrium showed secretory changes. Withdrawal of therapy releases the drug's inhibiting central effect, following which the mechanism of a normal menstrual cycle recurs, actively to terminate in true menstruation.

(4) As the first case demonstrates, subsequent to therapy, ovulation, conception, and progress of pregnancy were not influenced by Vallestril. Despite prolonged artificial inhibition of ovulation, pregnancy which followed Vallestril therapy was in no way deleteriously affected.

(5) As noted by Holmstrom,[18] a daily dose of 15 to 60 mg. is not required to effect inhibition of ovulation; 3 to 6 mg. daily by mouth is quite sufficient.

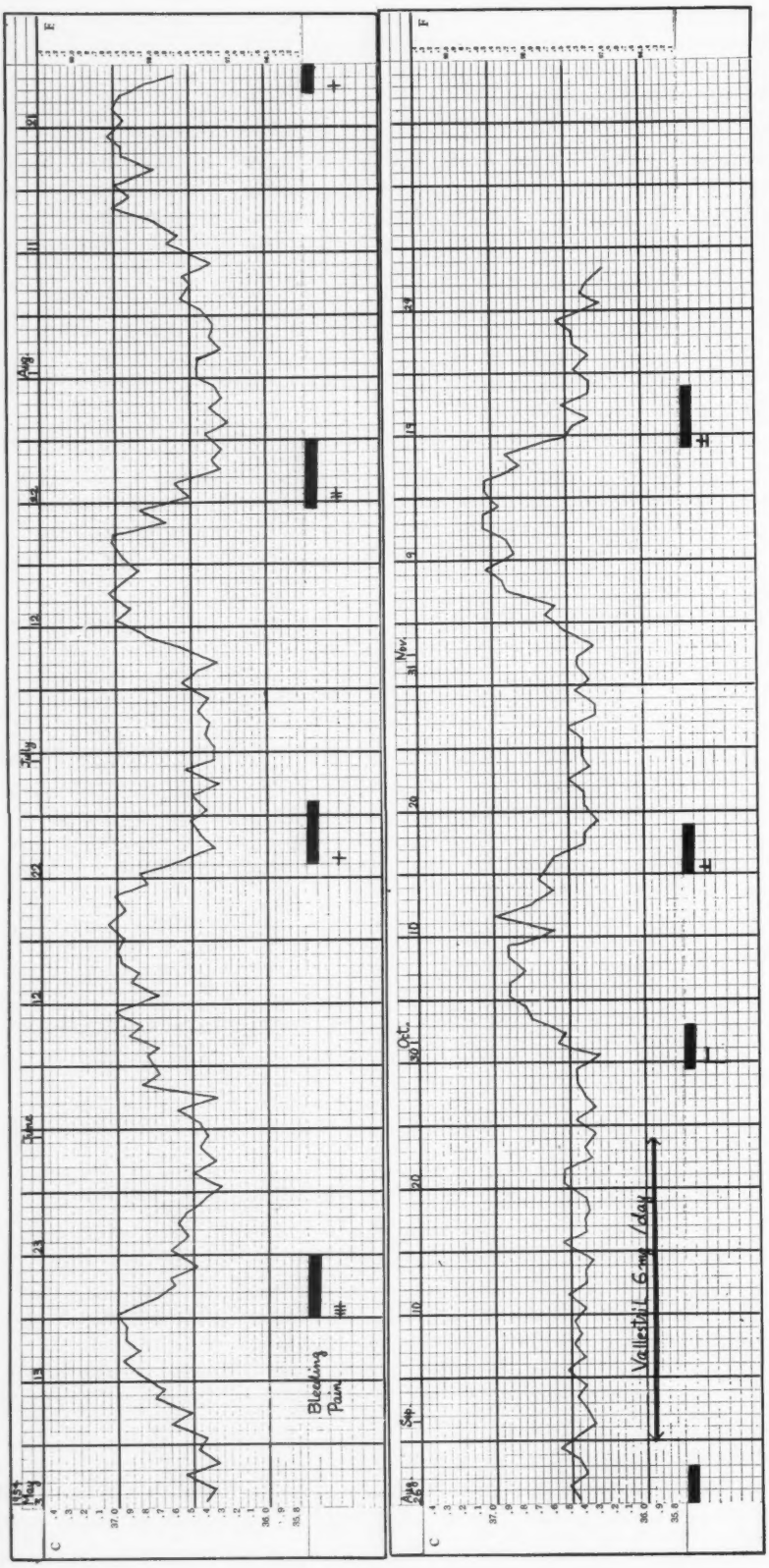

Fig. 4.—Second case. Basal body temperature curve following oral administration of Vallestril to a 21-year-old woman with functional dysmenorrhea.

This can be assessed, other than by clinical results, by comparison of blood estrogen levels during a physiologic menstrual cycle and artificial levels effected by estrogen therapy in castrated subjects.

(6) The beneficial effects with relief or disappearance of pain accompanying Vallestril withdrawal bleeding are but temporary.

4. Senile Vaginitis.—Frequently *Trichomonas vaginalis* infestation may be demonstrated in the vaginal discharge seen with senile vaginitis, so that clinical cure cannot be expected by estrogen therapy alone. Hence, in the present experiment, cases with Trichomonad infestation were ruled out. Vallestril was administered to 10 patients by either oral or vaginal route alone or by combined routes, and was effective in all cases. The vaginal insertion of a suppository was made only once daily or every second day, and caused no irritative symptoms. Vaginal smears showed a marked increase in superficial cells within four days of the administration of a 3 mg. Vallestril suppository every second day. This response is noted after 3 to 4 days when

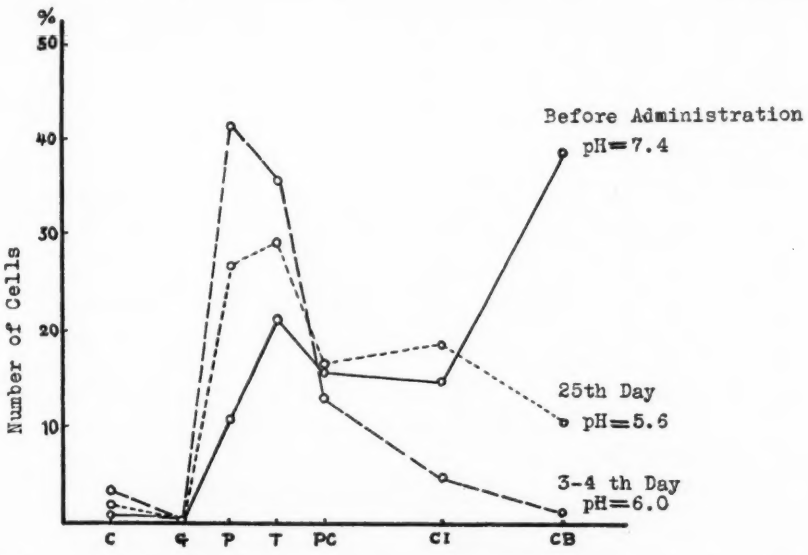

Fig. 5.—Vaginal smears of a patient with senile vaginitis following oral administration of Vallestril, 6 mg. daily for 6 days.

C, Fully cornified type
G, Granular
P, Pyknotic
T, Transitional
PC, Precornified
} Superficial squamous type
CI, Cells in intermediate type
CB, Cells in outer and inner basal type

6 mg. of Vallestril is given daily for three days by mouth (Fig. 5). When either type of medication is discontinued, there remains a preponderant increase in superficial cells as compared to cells of the intermediate and basal layers, and cells showing atrophic changes are already evident. Administration of Vallestril resulted in improved vaginal cytology, decreased leukorrhea and decreased vaginal pH, along with alleviation of clinical symptoms. In cases complicated by *Trichomonas vaginalis* infestation, specific trichomonicidal therapy is, of course, concomitantly indicated.

5. Prepubertal Vulvovaginitis.—Marked improvement in symptoms and vaginal cytology was noted within seven days after oral administration of 1.5 to 6.0 mg. daily, to a total dose of 3 to 27 mg., to a group of children aged

2 to 9 with vulvovaginitis. This investigation is interesting from the viewpoint of clinical effectiveness of estrogenic substances for vulvovaginitis, as well as their estrogenic action on vaginal epithelium. Administration of a single dose of 1.5 mg. of Vallestril produces no significant changes, whereas 3.0 mg. will produce a definite increase in superficial cells (Fig. 6). This effect is marked when 3 to 6 mg. is given daily for 4 days (Fig. 7). As illustrated in Fig. 6, following a 3 mg. dose, there is a rapid transition in vaginal cytology; after 72 hours, the cellular picture is exactly similar to that seen in estrus, and is present even on the eleventh day. Administration of 6 mg. daily for 4 days will maintain the cytologic picture of estrus for 6 to 15 days. Return to the premedication picture is seen only at about the thirtieth day following administration.

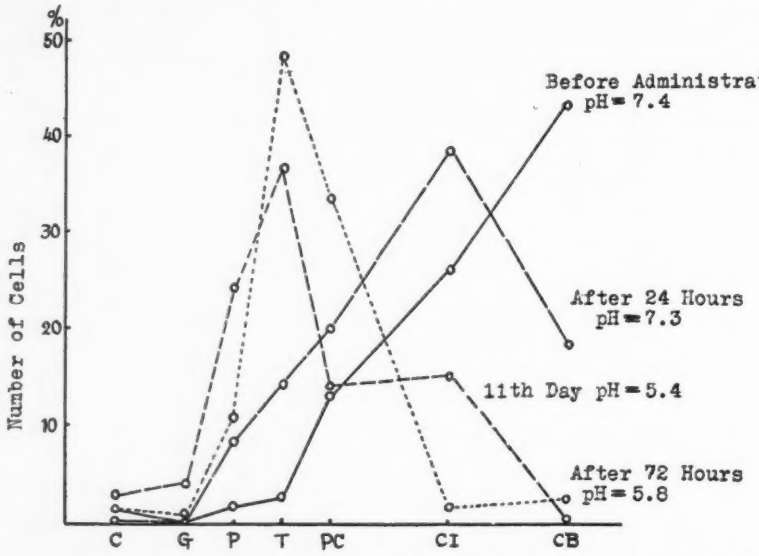

Fig. 6.—Vaginal smears of a patient with prepubertal vaginitis following oral administration of a single 3 mg. dose of Vallestril.

C, Fully cornified type
G, Granular
P, Pyknotic
T, Transitional
PC, Precornified
} Superficial squamous type
CI, Cells in intermediate type
CB, Cells in outer and inner basal type

6. Suppression of Lactation.—Daily oral doses of the order of 6 to 15 mg., to totals of 24 to 75 mg., were administered to 10 women in whom suppression of lactation was indicated because of stillbirth or neonatal fetal death. Vallestril constituted the only treatment procedure and was instituted when patients complained of breast engorgement. Mastodynia disappeared within 2 to 5 days of the institution of therapy and was followed by diminished lactation. Van den Driessche[11] administered 3 ampules of Vallestril, each containing 0.75 mg., 24 to 48 hours after delivery; thereafter medication was given every other day. Clinical relief of engorgement was noted after the second injection and complete relief of pain at the time of the third injection. In the present series, however, three to five times the dose employed by van den Driessche was given, since in comparison other synthetic estrogens such as Euvestin[20] and Robal[36] were equally effective in daily parenteral doses of 50,000 to 100,000 I.U. It is thought that oral dosage employed in the present series is quite adequate in view of the comparative blood estrogen levels produced by each of the assessed substances, detailed in Section I.

7. Menopausal Disorders.—Vallestril administered to 22 patients suffering from menopausal disorders effected relief of headache, myalgias, vertigo, vasomotor symptoms, and psychic disturbances, but had little effect on tinnitus and arthralgia. Because of the complexity of factors, organic and psychic, entering into the formation of menopausal disorders, individual and variable therapeutic responses may be anticipated, and, where hormone therapy is employed, route and dose of medication must be highly individualized.

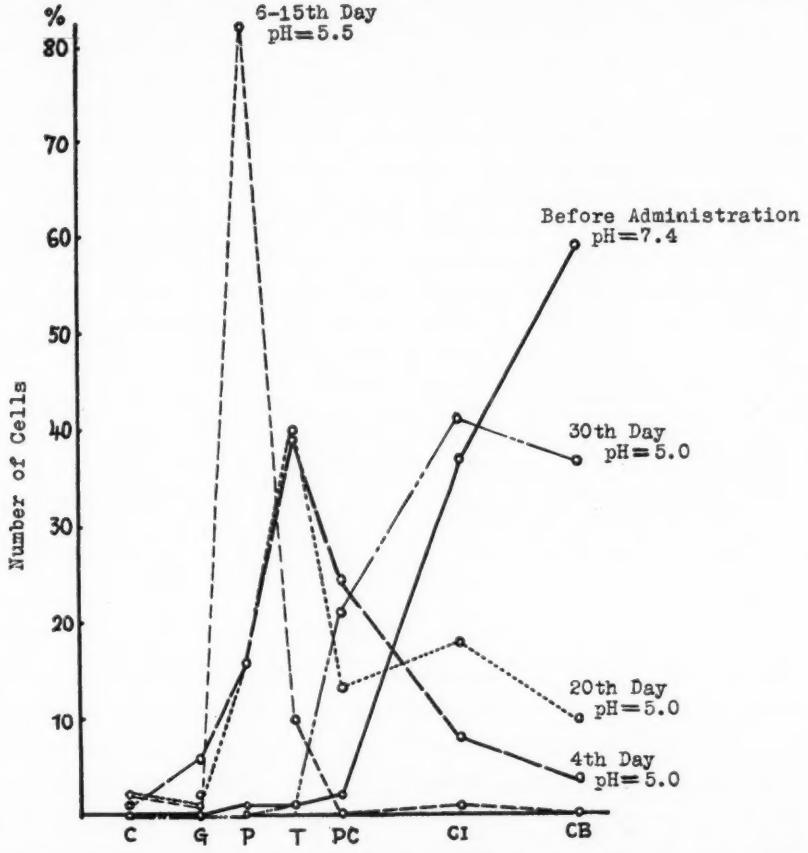

Fig. 7.—Vaginal smears of a patient with prepubertal vaginitis following oral administration of Vallestril, 6 mg. daily for 4 days.

C, Fully cornified type
G, Granular
P, Pyknotic
T, Transitional
PC, Precornified
} Superficial squamous type
CI, Cells in intermediate type
CB, Cells in outer and inner basal type

In the group given 6 to 12 mg. daily by mouth, clinical response appeared by the seventh day, whereas response was delayed to 3 to 4 weeks when 3 mg. was given daily. With neither schedule were abnormal bleeding nor deleterious side effects noted.

It is generally accepted that the menopausal disorders are not the results solely of diminished or absent ovarian function, but rather result from a pluriglandular imbalance affecting the entire body. Strictly speaking, therefore, effectiveness of estrogen therapy is not to be expected for every symptom of menopausal disorders; however, its effectiveness as a stimulative therapy would be taken into consideration. Namely, according to Netter,[28] Vallestril is

uncertain in relieving vasomotor symptoms and is also inferior to estradiol benzoate in its general effect. In this series too, the importance of the influence of suggestion in alleviating the psychological component of disorders cannot be denied, hence assessment of clinical results is most difficult.

According to Sturnick and Gargill,[35] Vallestril must be administered in larger doses than such synthetic estrogens as stilbestrol and ethinyl estradiol and, if the drug is to be clinically effective, clinical response should be noted in 3 to 4 days, or at latest 7 days, after therapy is started. In these cases a marked increase in superficial cells and decreased vaginal pH were also noted as in cases of treated senile vaginitis.

8. Side Effects.—Minimal lower abdominal pain, diarrhea, nausea, and breast engorgement with mastodynia were noted as side effects. Diarrhea occurred in one patient given 153 mg., mastodynia in the patient given 45 mg., and nausea in 2 patients given 45 and 75 mg. These side effects occurred in the group with amenorrhea. The remainder of the side effects observed were in the functional bleeding group, variable headache in one patient treated with 18 mg., lower abdominal pain in 2 with 45 and 63 mg., diarrhea in 2 with 30 and 45 mg., and breast engorgement in one with 30 mg., 6 cases in all. All these were minimal and temporary, in no instance requiring cessation of therapy. Actually, Vallestril precipitated fewer side effects than other synthetic estrogen substances previously assessed,[20] within the limit of effective oral dose required to obtain desired clinical effects. Laboratory assessment did not show specific systemic derangements, confirming the low toxicity noted by Hambourger and associates[6] in animal experiments, and by Gargill,[14] who found no significant side effects with daily doses up to 12 mg. administered to either normal females or males for 6 to 8 weeks.

Comment

Vallestril produced as the methoxy compound of the dimethyl ethyl derivative of 6-hydro-oxynaphthalene-propionic acid by Horeau and Jacques[7] has been shown to possess estrogenic properties, the effectiveness of which has been compared to that of the dimethyl ethyl derivative. This estrogenic activity was confirmed in subcutaneous, oral, and intrasplenic administration by Courrier, Horeau, and Jacques.[2] Hambourger and co-workers[6] have reported on the extremely low toxicity of Vallestril. Comparison of the effect of one subcutaneous injection of Vallestril in oil preparation with those of other estrogens is summarized in Table VI.

Minimum oral doses of Vallestril in mice are of the order of 1.0 γ and in rats 4.0 γ; in the latter animal this dose is somewhat less potent than 1.5 γ of Robal.[36] As for comparable effects of Vallestril, the oral dose must be four times that of the subcutaneous dose. Percutaneous administration of Vallestril was able to maintain estrus for 2.8 days in dosage of 1.0 γ, by virtue of delayed absorption producing prolonged physiologic effect; this route of administration of Vallestril then is as efficacious as with other synthetic estrogens. Oral administration of 3 mg. of Vallestril results in rapid absorption from the upper gastrointestinal tract with detectable elevated blood estrogen levels after 3 hours, and with maximum levels after 12 hours. Maximum

blood estrogen levels could be maintained satisfactorily by daily oral administration of 3 mg. of Vallestril. This effect can be produced with Robal, in comparison, by daily intramuscular injection of 2.5 mg. of that preparation.

The clinical effectiveness of Vallestril was investigated in 110 cases with symptoms peculiar to the obstetric and gynecologic field and this preparation was found to be satisfactorily effective with few side effects as an estrogenic substance, in keeping with the noted experimental findings.

TABLE VI. COMPARISON OF THE EFFECT OF SUBCUTANEOUS VALLESTRIL WITH OTHER ESTROGENIC PREPARATIONS

PREPARATION	SOURCE OF REPORT	MAXIMUM DOSE TO INDUCE ESTRUS	
		MOUSE (γ)	RAT (γ)
Natural Estrogens and Derivatives.—			
Estrone	Ito et al.[38]	0.3	2.0
	Furuya et al.	0.1	0.5
Estrone benzoate	Ito et al.	0.16	1.25
Estradiol benzoate	Ito et al.	0.04	0.1
Estradiol valerianate	Furuya et al.	0.025	---
	Furuya et al.	0.02	---
Synthetic Estrogens.—			
Diethylstilbestrol	Ito et al.	0.1	0.5
	Onagi[10]	---	0.25
	Furuya et al.	0.1	0.25
Diethylstilbestrol propionate	Ito et al.	0.06	0.25
	Onagi	---	0.3
Diethylstilbestrol acetate	Ito et al.	0.06	0.25
Robal	Tsukahara[36]	0.3	0.2
Vallestril	Furuya et al.	0.4	1.4

Summary and Conclusions

1. The chemical structure and estrogenic activity of a naphthalene compound, allenolic acid, and its derivatives have been discussed.

2. The estrogenic activity of 3-(6-methoxy-2-naphthyl)-2-2-dimethyl pentanoic acid (Vallestril), an allenolic acid derivative, was investigated with spayed mature mice and rats employed as test animals.

3. The minimum dose of Vallestril to produce estrus by subcutaneous injection is 1.0 γ in the rat and 0.4 γ in the mouse; by oral administration it is 4.0 γ and 1.0 γ, respectively. Percutaneous administration of 1.0 γ of Vallestril results in maintenance of estrus for an average of 2.8 days.

4. Oral administration of 3 mg. of Vallestril produces maximum blood estrogen levels in a 12 hour period, with rapid decline after 24 hours. The maximum level corresponds to the maximum level found 12 hours after the intramuscular injection of 2.5 mg. of Robal.

5. A new synthetic estrogen, Vallestril, was assessed clinically in certain obstetric and gynecologic disorders.

6. Vallestril by oral and vaginal suppository routes was employed in 29 cases of amenorrhea, 30 cases of functional uterine bleeding, 10 cases of senile

vaginitis, 2 cases for inhibition of ovulation, 7 cases of prepubertal vulvovaginitis, 10 cases for suppression of lactation, and in 22 cases of menopausal disorders—a total of 110 cases in which its effectiveness was confirmed.

7. Few side effects were encountered which were serious or required interruption of therapy.

8. Vallestril is a new synthetic estrogen with few side effects and is quite effective by oral administration.

We wish to acknowledge the constant support given to us by Professor T. Hasegawa, Chief of the Department of Obstetrics and Gynecology, University of Tokyo School of Medicine. Thanks are due to Drs. N. Kawai and M. Tsuno, and Dr. T. Kon and Mr. K. Ishihara of the Sanzen Pharmaceutical Oumiya Institute, Japan.

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References

1. Cook, J. W., Dodds, E. C., and Hewett, C. L.: Nature **131**: 56, 1933.
2. Courrier, R., Horeau, A., and Jacques, J.: Compt. rend. Acad. sc. **224**: 1401, 1947.
3. Courrier, R., Horeau, A., and Jacques, J.: Compt. rend. Soc. biol. **141**: 159, 1947.
4. Courrier, R., Horeau, A., and Jacques, J.: Compt. rend. Soc. biol. **141**: 747, 1947.
5. Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.: Nature **142**: 34, 1938.
6. Hambourger, W. E.: Personal communication, 1954.
7. Horeau, A., and Jacques, J.: Compt. rend. Acad. sc. **224**: 862, 1947.
8. Julia, S.: Thèse, Série A, No. 2356, 1951, présenté à la faculté de science de l'université de Paris.
9. Kobayashi, T., and Nakayama, T.: Conference of Endocrinology (Japan) **2**: 465, 1952.
10. Onagi, M.: Nippon Huzinka Gk. Z. (Japan) **37**: 893, 1942.
11. Van den Driessche, R.: Ann. d'endocrinol. **9**: 278, 1948.
12. Fluhmann, C. F.: Surg., Gynec. & Obst. **52**: 1051, 1931.
13. Furuya, H., Deguchi, K., and Shima, M.: J. Japan. Obst. & Gynec. Soc. (English edition) **1**: 373, 1954.
14. Gargill, S. L.: Personal communication, 1953.
15. Gennes, L., Bricaire, H., and Tubiana, M.: Bull. et mém. Soc. méd. hôp. de Paris **64**: 289, 1948.
16. Hamblen, E. C.: Endocrinology **20**: 769, 1936.
17. Hambourger, W. E.: Personal communication, 1954.
18. Holmstrom, E. G.. Personal communication, 1952.
19. Izuchi, S., et al.: References Concerning Vallestril, Dainippon Pharmaceutical Company **1**: 13, 1955.
20. Iwai, S., Furuya, H., and Suzuki, T.: Exper. Therap. (Japan) **241**: 7, 1948.
21. Johnson, C. G.: Personal communication, 1952.
22. Miescher, K., et al.: Helvet. chim. acta **27**: 1727, 1944.
23. Miescher, K., and Heer, J.: Helvet. chim. acta **28**: 156, 1945.
24. Miescher, K., and Heer, J.: Helvet. chim. acta **31**: 1289, 1948.
25. Miescher, K., and Anner, G.: Helvet. chim. acta **31**: 2173, 1948.
26. Miescher, K., and Anner, G.: Helvet. chim. acta **32**: 1957, 1949.
27. Narita, F., Tanaka, S., and Shimanuki, T.: Obst. & Gynec. (Japan) **21**: 11, 1954.
28. Netter, A.: Bull. et mém. Soc. méd. hôp. de Paris **64**: 100, 1948.
29. Okuda, H., and Kimura, H.: References Concerning Vallestril, Dainippon Pharmaceutical Company **1**: 9, 1955.
30. Remesow, I.: Recueil des travaux chimiques des Pays-Bas. **55**: 797, 1936.
31. Robinson, R., Cornforth, J. W., and Cornforth, R. H.: J. Chem. Soc. London, part 2, 689, 1942.
32. Ruzicka, L., Müller, P., and Mörgeli, E.: Helvet. chim. acta **21**: 1394, 1938.
33. Sagawa, S., et al.: References Concerning Vallestril, Dainippon Pharmaceutical Company **1**: 34, 1955.
34. Saito, H.: J. Japan. Obst. & Gynec. Soc. (Japanese edition) **6**: 241, 1954.
35. Sturnick, M. I., and Gargill, S. L.: New England J. Med. **247**: 829, 1952.
36. Tsukahara, S.: J. Japan. Obst. & Gynec. Soc. (Japanese edition) **4**: 965, 1952.
37. Wieland, P., and Miescher, K.: Helvet. chim. acta **31**: 1844, 1948.
38. Ito, M., Ueno, F., and Akamatu, S.: Nippon Huzinka Gk. Z. (Japan) **36**: 958, 1941.

Case Reports, New Instruments and Methods

PREGNANCY COMPLICATED BY NEPHROTIC SYNDROME

A Case Report

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(From the Obstetrical Service of Bronx Hospital, in cooperation with the Medical Service)

THE nephrotic syndrome in pregnancy is very rare. In his excellent text Dieckmann[1] states that he has not observed a proved case since 1940. He reports an incidence of acute or chronic glomerulonephritis and nephrosis in association with pregnancy of less than 0.1 per cent. Nephrosis with pregnancy was reported by Wegner[2] in 0.028 per cent of cases and by Eastman[3] in 0.027 per cent. Several isolated instances of lipoid nephrosis in adults who recovered and subsequently had normal pregnancies appear in the literature.[4, 5] Other cases of nephrosis with the onset during pregnancy have been reported.[6]

Nephrosis may be one aspect of glomerulonephritis, or it may be a separate disease entity.[7-9] It should perhaps be referred to as the "nephrotic syndrome" until its nature is more clearly defined. Accordingly, no attempt has been made in this paper to differentiate the hypoproteinemic stage of glomerulonephritis from so-called "true lipoid nephrosis."

The nephrotic syndrome generally begins insidiously. Unlike acute glomerulonephritis it is not usually preceded by an acute infectious disease. It is characterized by generalized edema, massive proteinuria, and occasional casts and leukocytes in the urinary sediment; hematuria is rare. Hypertension is absent. Characteristic findings in the blood are a reduction in the total plasma protein with hypoalbuminemia and hypercholesterolemia but with little or no nitrogen retention. Renal excretion tests are usually normal.[10, 11]

This report is concerned with the nephrotic syndrome in a young pregnant woman and is of particular interest because of the favorable outcome of the pregnancy.

Case Report

E. E. (Bronx Hospital No. 292409), a 15-year-old Negro girl, gravida i, para 0, was admitted for the third time to the Bronx Hospital and for the first time to the Obstetrical Service in the third month of pregnancy on Sept. 22, 1955. The last menstrual period was on June 10, 1955, and the estimated date of confinement was March 17, 1956.

First Admission.—Her first Bronx Hospital admission had taken place on Sept. 24, 1953, 2 years previously, at the age of thirteen because of progressive swelling of the legs and eyelids for 8 months; slight redness of urine was noticed by the patient on the day of admission. No preceding infection was recalled by the patient. The past medical history disclosed only pertussis, measles, and chicken pox in early childhood.

Physical examination at that time showed a well-nourished female patient with a normal temperature and in no great discomfort. The blood pressure was 125/85. The only abnormal sign was edema of the eyelids and both lower extremities.

The hemoglobin was 10.2 Gm. per cent; erythrocytes 3.7 million; leukocytes 8,000 with a normal differential count. The specific gravity of the urine was 1.020, albumin 3 plus; very occasional red and white blood cells and a few fine granular casts were present; there was no glycosuria. The erythrocyte sedimentation rate was 42 mm. per hour (Wintrobe). The blood urea nitrogen was 11 mg. per cent; cholesterol 774 mg. per cent; total serum proteins 4.1 Gm. per cent (albumin 1.6, globulin 2.5); serum creatinine 0.8 mg. per cent. Serologic tests for syphilis were negative.

Therapy consisted of bed rest, low-salt diet, oral penicillin, and ACTH, 25 mg. intramuscularly every 6 hours. Diuresis began within 24 hours after the institution of hormone therapy. By the time of her discharge from the hospital 17 days later her weight had fallen from 132 to 108 pounds, the edema had disappeared, and the urine contained only a trace of albumin. The urea clearance was 77 per cent of normal, and serum proteins had returned to normal values (total proteins 7.2 Gm. per cent, albumin 4.9, globulin 4.3). Serum cholesterol was 405 mg. per cent. The blood pressure remained normal. She was discharged on a low-salt diet and oral penicillin with the diagnosis of "nephrotic stage of glomerulonephritis."

Second Admission.—Two weeks after discharge she was readmitted to the Medical Service of the Bronx Hospital because of edema of the face and extremities associated with a 20 pound weight gain. The blood pressure was normal, hemoglobin 9.9 Gm. per cent, erythrocytes 3.2 million, leukocytes 5,000. Urinalysis (catheterized) showed a 4 plus proteinuria with varying numbers of white but no red blood cells. The blood urea nitrogen was 7 mg. per cent, and the serum cholesterol varied between 600 and 850 mg. per cent. The albumin-globulin ratio was 2.2:3.1 on admission, 2.0:3.9 one week after admission, and 2.8:2.5 on discharge. X-ray of the chest suggested the presence of a small amount of fluid in the right costophrenic angle.

The patient was placed on the previous hospital regime except for hormone therapy. During the following 2 weeks the weight decreased from the initial 128 pounds to 119 pounds. At that time oral cortisone was started (300 mg. on the first day, 200 mg. on the second, and 100 mg. daily thereafter). Further diuresis occurred, the weight was stabilized at 114 pounds, and the proteinuria diminished to 1 plus. Cortisone was reduced to 50 mg. per day, and the patient was discharged on the previous dietary regime, cortisone, and oral penicillin.

Thereafter the patient moved away and was followed by a physician in the South who subsequently reported no pathologic findings. Urinalyses were stated to have been normal. Apparently, she abandoned the diet as well as the prophylactic antibiotics and steroid therapy at that time.

Third and Fourth Admissions.—Two years later, on Sept. 22, 1955, she returned for the third time to the Bronx Hospital for admission to the Obstetrical Service. The general condition of the patient appeared to be satisfactory; there was no acute distress. The normal signs of the first trimester of pregnancy were present, and there was no evidence of localized or generalized edema. Urinalysis showed a specific gravity of 1.013 and a trace to 1 plus proteinuria. Blood chemistry determinations were within normal limits except for the cholesterol which was 326 mg. per cent. Urinary concentration and dilution tests were within normal limits, as was the phenolsulfonphthalein excretion. Ophthalmologic examination disclosed normal fundi. Because of the good general condition, minimal evidence of renal involvement, and the duration of gestation, it was decided to allow her to continue to term. On Oct. 7, 1955, two weeks after admission, she was discharged for follow-up at weekly intervals in the prenatal clinic. During the following months the patient was seen regularly and continued to do well. She had no edema, and blood pressure averaged 120/70. Urinalyses continued to show a trace to 1 plus albumin.

On Feb. 2, 1956, in the eighth month of pregnancy, urinalysis showed a 4 plus proteinuria. She was immediately hospitalized (fourth Bronx Hospital admission). Examination disclosed a moderate hydramnios but no systemic edema or hypertension. Two to 4 plus proteinuria persisted. She had one episode of epistaxis but otherwise continued to do well. The total serum protein was 5.3 Gm. per cent, total cholesterol 435 mg. per cent, and the sedimentation rate was 117 mm. at the end of one hour (Westergren).

On Feb. 27, 1956, at 37 weeks' gestation, spontaneous labor occurred, and after 21 hours she was delivered without difficulty of a living baby girl in good condition, 18 inches long and weighing 5 pounds, 8 ounces. A right mediolateral episiotomy was performed under light nitrous oxide-oxygen-ether anesthesia.

During the postpartum period the patient felt well and had no complaints. At this time daily urinalyses showed a persistent 4 plus proteinuria. Total serum protein was 4.7 Gm. per cent (albumin 2.3, globulin 2.4). Uric acid was 7.0 and 5.2 mg. per cent and total cholesterol 398 mg. per cent.

Six weeks post partum, routine examination in the postnatal clinic revealed mother and baby to be in good health. The mother had no edema, the blood pressure was normal, and the urine showed 1 plus albumin but no casts. Blood chemistry values were as follows: cholesterol 376 mg. per cent, total serum protein 5.4 (albumin 2.8, globulin 2.6). She was continuing on a low-salt, high-protein diet but was not taking steroid or antibiotic medication for prophylaxis.

Fifth Admission.—Two months post partum, on May 3, 1956, she was admitted to the hospital for the fifth time because of swelling of the legs for four days and puffy eyes for one day. She had had an upper respiratory infection 3 weeks previously.

Physical examination disclosed no abnormalities other than puffy eyelids and sacral and bilateral pretibial edema. The blood pressure was 130/80. Laboratory findings were as follows: hemoglobin 10.2 Gm. per cent with a normal total and differential white cell count. Urinalysis showed 4 plus proteinuria on admission. A urine concentration test disclosed maximum concentration of 1.012. The dilution test was normal. The sedimentation rate was 118 mm. per hour (Westergren), blood urea nitrogen 18 mg. per cent, blood sugar 95 mg. per cent, serum proteins 4.8 Gm. per cent (albumin 1.9, globulin 2.9). The serum cholesterol was 530 mg. per cent. Serum electrolytes were well within normal limits. The serum antistreptolysin titer was less than 50 units per cubic centimeter.

Systemic penicillin was administered and the previous dietary regime instituted. After 3 days of observation no change occurred in her condition. Prednisone, 30 mg. daily, was begun, and considerable diuresis started within 36 hours of therapy. With this diuresis the weight fell from 144 to 117 pounds, and there has been a fairly rapid and complete clearing of the proteinuria. At the time of this writing, May 21, 1956, serum protein values have changed but slightly: total proteins 4.3, albumin 2.0, globulin 2.3. Steroid dosage is being reduced gradually.

Comment

This patient had a well-documented nephrotic syndrome, presumably due to chronic glomerulonephritis. Her general condition during the first and second trimesters of pregnancy was excellent, and there was no evidence of renal insufficiency. Mild elevation of serum cholesterol was the only abnormality suggestive of continuing disease. The occurrence of edema and proteinuria in the eighth month might have been confused with toxemia of pregnancy, but the hypoproteinemia, hypercholesterolemia, and lack of nitrogen retention and hypertension served as adequate distinguishing criteria.[10]

Physiologic alterations of renal function in normal pregnancy seem to be minimal.[1, 12, 13] It is difficult, therefore, to estimate the role of the pregnancy in exacerbation of the nephrotic syndrome. The exacerbation two months post partum was apparently unrelated to the pregnancy and may be attributed in part to a preceding respiratory infection.

Summary

A case is presented in which pregnancy was complicated by recurrence of the nephrotic phase of chronic glomerulonephritis. There was a normal full-term delivery of a healthy infant. The patient had a remission post partum, followed by another, unrelated exacerbation.

We wish to express our appreciation to Dr. Edward E. Fischel, Director of the Department of Medicine, Bronx Hospital, for his advice.

References

1. Dieckmann, W. J.: The Toxemias of Pregnancy, ed. 2, St. Louis, 1952, The C. V. Mosby Company.
2. Wegner, C. R.: Am. J. Obst. & Gynec. 33: 51, 1937.
3. Eastman: Cited by Dieckmann.[1]
4. Barach and Boyd: Cited by Dieckmann.[1]
5. Epstein, A. A.: Bull. New York Acad. Med. 13: 621, 1937.
6. Pigeaud, H., and Contamin, R.: Lyon méd. 155: 573, 1935.
7. Fishberg, A. M.: Hypertension and Nephritis, ed. 5, Philadelphia, 1954, Lea & Febiger.
8. Ellis, A.: Lancet 1: 1, Jan. 3, Jan. 10, Jan. 17, 1942.
9. Allen, A.: Am. J. Med. 18: 277, 1955.
10. Cecil, R. L., and Loeb, R. F.: Textbook of Medicine, ed. 9, Philadelphia, 1955, W. B. Saunders Co.
11. Bradley, S. E., and Tyson, C. J.: New England J. Med. 238: 223, 1948.
12. Chesley, L. C.: M. Clin. North America 35: 699, 1951.
13. Mussey, E.: M. Clin. North America 35: 1051, 1951.

PUERPERAL INVERSION OF THE UTERUS OCCURRING IN CONSECUTIVE PREGNANCIES IN THE SAME PATIENT

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PUERPERAL inversion of the uterus is a dangerous, uncommon complication of pregnancy and delivery. The cardinal symptoms of acute inversion are shock and hemorrhage. The degree of shock is out of proportion to the blood loss. Recovery occurs quickly when the shock is treated and there is replacement of the uterus in its correct position.

A case is presented in which puerperal inversion occurred in the same patient in consecutive pregnancies. The cause was undetermined in both instances. The first pregnancy presented the added complication of spontaneous rupture of the uterus during delivery.

Case Report

This 21-year-old white gravida i, para 0, was at term on Sept. 17, 1953. She was admitted to the labor room at 8:30 A.M. on Sept. 21, 1953, with spontaneous rupture of the membranes. The pains were every 3 minutes, lasting 35 seconds. The blood pressure was 110/70, pulse 80, and temperature normal. Examination showed a left occipitoanterior position, with the presenting part at 0 station. The cervix was 70 per cent effaced and 4 cm. dilated. The fetal heart tones were 140 per minute. Rectal examination at 9:30 A.M. showed 5 cm. dilatation. Demerol, 100 mg., and vitamin K, 10 mg., were given. At noon the cervix was completely dilated and the head was on the perineum. The patient was transferred to the delivery room. At 12:27 P.M. a female infant who weighed 7 pounds, 8 ounces, was born spontaneously with episiotomy under nitrous oxide and cyclopropane anesthesia. One cubic centimeter of Ergotrate was given intramuscularly. The placenta was not ready to be expelled, so the episiotomy was repaired. The uterus was boggy during the repair and there was a continuous ooze of blood. The blood pressure was 130/80 and the pulse was 84. At 1:10 P.M. the placenta was delivered spontaneously, accompanied by a large gush of blood and clots. The uterus was palpated abdominally and found to be boggy and one finger below the umbilicus. One cubic centimeter of Pitocin was given intramuscularly and 1 c.c. of Ergotrate intravenously. The blood pressure dropped to 80/40; the pulse was 110 and irregular. An infusion of glucose in water was started and 1 c.c. of Methedrine was given into the vein. At 1:40 P.M. Neo-Synephrine, 0.3 c.c., was given intravenously and the blood pressure rose to 106/70. The pulse continued to be thready and rapid. The uterus appeared firm, one finger below the umbilicus, but uterine bleeding continued. The skin of the patient was cold, moist, and the anesthetist was unable to elicit any blood pressure. Five cubic centimeters of adrenal cortex was given intravenously. By 3:00 P.M. 1,000 c.c. of whole blood had been given through multiple sites. The patient's condition improved enough so a sterile vaginal examination could be made. A complete inversion of the uterus was found, with the cervix pulled up under the symphysis pubis. The uterus continued to bleed profusely. Palpation disclosed a rent in the left lateral portion of the corpus 6 cm. in length. The patient continued in deep shock; the pulse was thready; the blood pressure was not obtainable, and the patient's condition so poor that it was felt further uterine manipulation was not advisable. She was

transferred to the operating room by 4:30 P.M. Blood pressure and pulse were not obtainable, but after abdominal incision was made the aorta was palpated and the pulse found. Anesthesia consisted of cyclopropane-oxygen. Examination showed the uterus to be completely inverted, with the ovaries and the round ligaments pulled into the crater the inversion created. There was about 100 c.c. of free blood in the peritoneal cavity, which had come from the 6 cm. tear in the left lateral wall of the uterus. There was no active bleeding from the rent. The round ligaments were grasped with ring forceps and the uterus returned to its normal position. Almost immediately the pulse was palpable in the radial artery and the blood pressure rose to 70/40, then to 140/80, and the pulse was counted at 110 per minute. The tear in the uterus was repaired and the abdomen closed. Three additional pints of blood were given during the time the patient was in the operating room, which she left in good condition. Following operation the hemoglobin was 8 Gm. per 100 c.c. of blood, and the red blood count 2.8 million per cubic millimeter.

Twenty-four hours post partum another unit of blood was given, a total of 8 pints in all since the patient had been delivered. At 48 hours post partum the hemoglobin was 10.5 Gm. and the red blood count was 3.8 million. The patient made an uneventful recovery without morbidity.

The same patient was again at term on March 3, 1956. She was admitted to the labor room at 11:00 P.M., March 15, 1956, with spontaneous rupture of the membranes at home. Active labor began at 2:00 A.M., March 16. The pains were every 4 minutes, lasting 30 to 40 seconds. The blood pressure was 130/80, pulse 84, and temperature normal. Examination showed vertex presentation, left occipitoanterior position, with the presenting part at minus 1 station. The cervix was 4 cm. dilated. The fetal heart tones were 140 per minute. Demerol, 100 mg., was given intramuscularly. At 4:30 A.M. a rim of cervix remained and the patient was taken to the delivery room. At 4:50 A.M., a female infant who weighed 9 pounds, 1 ounce was delivered by low forceps with episiotomy under nitrous oxide-oxygen anesthesia. One cubic centimeter of Ergotrate was given intramuscularly following delivery of the infant. The placenta was not ready to be expelled, although bleeding from the uterus was rather profuse. The uterus appeared boggy and was found to be one finger below the umbilicus. At 5:05 A.M. manual exploration of the uterus was done and the placenta was found to be adherent to the posterior wall of the uterus and the uterus to be inverted, with the cervix pulled up under the symphysis. The uterus was manually replaced in its normal position and the placenta removed. An infusion of ⅙ molar lactate solution was started, followed by 500 c.c. of blood. The blood pressure dropped to 66/40 and the pulse was 112 during the procedure. When the uterus was replaced, the blood pressure rose to 100/60 and the pulse dropped to 90. On March 16, 1956, the hemoglobin was 7.6 Gm. per 100 c.c. and the red blood count was 3.05 million. Another 1,000 c.c. of whole blood was given. The mother and infant made an uneventful recovery.

Comment

This case illustrates puerperal inversion of the uterus occurring twice in the same patient, without any known etiological factor. The presenting symptoms were excessive blood loss and shock. The consistent finding was shock out of proportion to blood loss. Blood and supportive treatment were not effective until the uterus had been replaced. Recovery promptly followed replacement of the uterus in its normal position.

Spontaneous rupture of the uterus during labor or delivery without a causative factor is uncommon. Most cases are associated with multiparity, previous scars of the corpus, cervical or myomectomy scars, large infants, or abnormal implantation of the placenta. In this case there was no previous history to suggest a complication of such magnitude.

Summary

1. A case is presented in which the uncommon complication of puerperal inversion occurred in successive pregnancies in the same patient.

2. There was no mismanagement of the third stage in either instance.

3. In these two deliveries the diagnosis of inversion could not be made by abdominal palpation.

4. In both deliveries, recovery from shock promptly followed replacement of the uterus in its normal position.

References

1. Bell, J. E., Wilson, G. F., and Wilson, L. A.: AM. J. OBST. & GYNEC. 66: 767, 1953.
2. Brierton, J. F.: AM. J. OBST. & GYNEC. 59: 113, 1950.
3. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc., p. 923.
4. Henderson, H., and Alles, R. W.: AM. J. OBST. & GYNEC. 56: 133, 1948.
5. Lull, C. B., and Kimbrough, R. A.: Clinical Obstetrics, Philadelphia, 1953, J. B. Lippincott Company, p. 354.

MASSIVE RETROPERITONEAL HEMORRHAGE DUE TO RUPTURE OF OVARIAN VEIN FOLLOWING NORMAL DELIVERY

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MASSIVE intra-abdominal hemorrhage associated with pregnancy and due to rupture of uteroovarian veins is always an unexpected catastrophe. Only by keeping this possibility in mind can we avoid delay in treatment and thereby prevent maternal deaths.

Unlike other cases of this type reported, in this case the hemorrhage did not involve the pelvic organs or ligaments.

R. P. (No. 120114) was a 24-year-old white gravida iii, para ii, whose expected date of confinement was July 15, 1955. Her prenatal course had been normal. She was admitted as a private patient at 11:00 A.M. on Aug. 1, 1955, because of a bloody show. The patient was delivered of a 7 pound, 7 ounce girl spontaneously at 6:00 P.M. that day after a total labor of 3 hours and 30 minutes. An episiotomy was done and repaired. The uterus contracted well with less than average blood loss resulting from the delivery. The patient's condition remained apparently normal until about 4:30 P.M. the following day. At that time, she complained of left flank pain and vertigo. The patient appeared apprehensive, pale, and was perspiring profusely.

On examination, the heart and lungs were normal, the uterus well contracted; there was questionable fullness in the left flank and left lower quadrant; the blood pressure was 80/50, pulse full, regular 82, and oral temperature 97° F.

She was given 1,000 c.c. of normal saline and a red blood count and hemoglobin determination obtained. The hemoglobin was 10 Gm. and the red blood count 3.4 millions. For a brief period the patient improved, but during the next three to four hours her condition became worse and it was apparent that she was in shock due to blood loss. She was given plasma substitutes while blood was being obtained.

At 11:20 P.M. on Aug. 2, 1955, an exploratory laparotomy was done. When the peritoneum was opened a small amount of dark blood was seen. The uterus was well contracted and pushed to the right by a large retroperitoneal hematoma on the left. This extended from above the left kidney downward to within 4 to 5 cm. of the base of the broad ligament. It was therefore apparent that a vessel had ruptured above the pelvis and did not directly involve the uterus or adnexa. The peritoneum overlying the mass was incised and handfuls of clots evacuated, estimated to be at least 2,000 c.c. of blood. A ruptured thin-walled vessel about 1 cm. in diameter was finally seen. This was so friable it was torn during the first attempt to ligate. From the characteristics and location of the vessel it was thought to be the left ovarian vein. The patient was given 1,500 c.c. of whole blood during the operation and an additional 500 c.c. the following day. The postoperative course was remarkably good. The most troublesome symptom was backache which was expected. The patient was discharged on the tenth postoperative day in good condition.

Comment

This patient's symptoms were relatively slow in developing if the rupture of the vessel occurred during labor or delivery as we believe to be the case. The fact that practically all the blood was confined to the retroperitoneal space and not intraperitoneal explains this to some extent. Bleeding confined to this area may well cease for periods of time only to begin again until finally obvious shock results. The important clue in this case was the left flank pain with fullness which could be palpated in a patient in shock.

The cause of rupture of uteroovarian veins associated with pregnancy seems to be increased venous pressure in greatly dilated veins of the pelvis. In this case, however, rupture occurred higher than usual, involving the ovarian vein above the pelvis.

Symptoms and signs will depend on the site of rupture as well as when it occurs. If the ruptured vein results in intraperitoneal hemorrhage the onset is apt to be sudden and to produce severe lower abdominal pain. If the bleeding is confined to the retroperitoneal space there will be low back or flank pain as in this case.

Summary

A case of rupture of an ovarian vein following a normal labor and spontaneous delivery is presented. The massive retroperitoneal hemorrhage which resulted did not involve the uterus, adnexa, or broad ligament. In this respect it was unique.

References

1. Conger, Sidney B., and Paternite, Carl J.: Am. J. Obst. & Gynec. **67**: 426, 1954.
2. Hodgkinson, C. P., and Christensen, R. C.: Am. J. Obst. & Gynec. **59**: 1112, 1950.
3. Jurishica, August J., and Gutglass, Milton: Obst. & Gynec. **6**: 315, 1955.

PHOCOMELUS: A CASE OF CONGENITAL MALFORMATION*

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PHOCOMELUS is a monster with rudimentary limbs, the hands and feet being attached almost directly to the trunk.[1] Potter[2] says that phocomelia is a rare malformation in which the hands and feet are attached to the trunk by single, small, irregularly shaped bones.

Because of the rarity of this malformation and the problems it presented in diagnosis and management, the following case is reported.

F. J. (Bronx Hospital No. 290940), a 29-year-old Negro, gravida v, para iii, had had three full-term, normal, spontaneous deliveries between 1949 and 1954. In 1952 she had had a spontaneous abortion in the third month of pregnancy. The menarche was at the age of 12 years with cyclic menses every 25 days, the flow lasting five days. Her first visit to the clinic in September, 1955, was for amenorrhea since her last normal period on July 1, 1955. There had been some staining in August, 1955. The expected date of confinement was April 8, 1956. An x-ray of the abdomen, taken on September 27 because the patient complained of a large abdomen, was reported as showing a single fetus of about five months' gestation. The size of the uterus was disproportionately larger than the size of the fetus would warrant, suggesting the presence of hydramnios. The patient was admitted to the hospital for the first time on Nov. 24, 1955, for investigation of polyhydramnios.

Physical examination showed a well-developed, well-nourished Negro woman in no acute distress. The positive physical findings were limited to the abdomen where pitting edema of the abdominal wall was noted. The abdomen was pendulous and tense. The fundus was palpated 2 fingerbreadths below the xiphoid process. The fetal heart tones were heard in the left flank. No ankle edema was observed. The blood pressure was 100/60 mm. Hg.

The past history, family history, and review of systems were noncontributory. The patient stated that during the early months of her pregnancy she had subsisted on a diet of vegetable salads and coffee. No infectious or viral diseases had been contracted during the first trimester of pregnancy or subsequently. There had been no exposure to x-rays other than the films taken at this hospital.

Urinalysis and blood chemistry determinations were within normal limits. The serologic test for syphilis was negative; the blood group was O, Rh positive.

On Nov. 25, 1955, an x-ray of the abdomen was reported as follows: "A single fetus in the breech position which has developed in accordance with the interval between Sept. 27 and Nov. 25, 1955. There is no evidence to suggest fetal death. The size of the uterus is much larger than the size of the fetus would warrant, but apparently hydramnios is present."

*Presented at a meeting of The Bronx Gynecological and Obstetrical Society, April 23, 1956.

The patient was discharged after three days of hospitalization and was followed in the clinic. On a visit to the prenatal clinic on December 8, fetal heart tones were no longer heard.

On Dec. 15, 1955, the patient was readmitted to the Bronx Hospital at 7:00 A.M. in labor. On rectal examination the presenting part was thought to be a breech at station minus 2; the cervix was 6 cm. dilated. and the membranes were intact. No fetal heart tones were heard. The patient was having strong contractions at 5 minute intervals.

Spontaneous rupture of the membranes occurred at 7:20 A.M., and abundant dark, bloody fluid was passed. Labor proceeded uneventfully. On rectal examination at 11:00 A.M. the presenting part could not be made out with certainty, and consequently a sterile vaginal examination was performed. The cervix was found to be fully dilated; rudimentary appendages, apparently feet, and a soft tissue mass were presenting. The head was in the left lower quadrant, and a diagnosis of transverse lie was made. An x-ray of the abdomen taken by a portable machine on the delivery table was unsatisfactory.

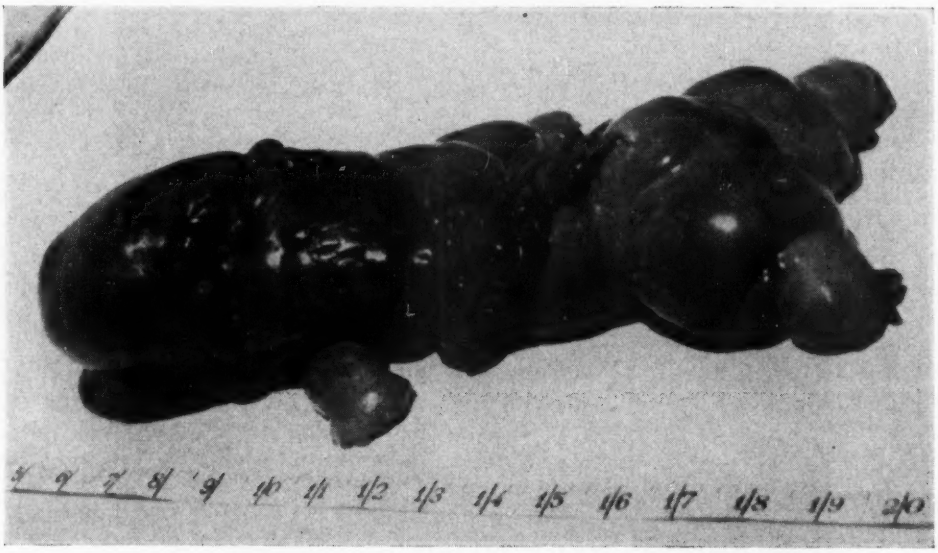

Fig. 1.—Phocomelus, showing rudimentary limbs and defective development of face.

Under deep gas-oxygen-ether anesthesia an internal version was attempted by guiding the head into the left upper quadrant and using external abdominal pressure to rotate the breech into the pelvis on the maternal right side. It was at this point that the anomalous lower limbs were diagnosed as such. Since the lower limbs could not be grasped well enough to apply traction, extraction was effected by the use of the Braun and Jardine hooks. The placenta was removed manually, and when manual exploration of the uterus disclosed no evidence of rupture, the organ was packed with 5 yards of iodoform gauze. The duration of the first stage of labor was five hours; the second stage lasted one hour and 20 minutes, and the third stage lasted five minutes. The mother had an uneventful postpartum course and was discharged on the fourth postpartum day.

Description of the Fetus (Fig. 1).—The weight was 5 pounds, 13 ounces, and the rump to crown length was 13 inches. The fetus was macerated and had an enlarged, malformed head with both eyes present. The external nares were absent; the hard palate had not fused in the midline and was split along its entire course. No posterior choanae were present. There were rudimentary ears as well as branchial clefts below the level of the tongue, which was present and formed. A portion of the mandible was missing in the midline. The region of the neck presented as an amorphous, fleshy mass.

The superior appendages were shortened with rudimentary forearms, hands, and fingers. A constriction ring was in evidence at the level of the wrist. The buds of five digits were present bilaterally. Bone tissue was palpable in the proximal part of both appendages.

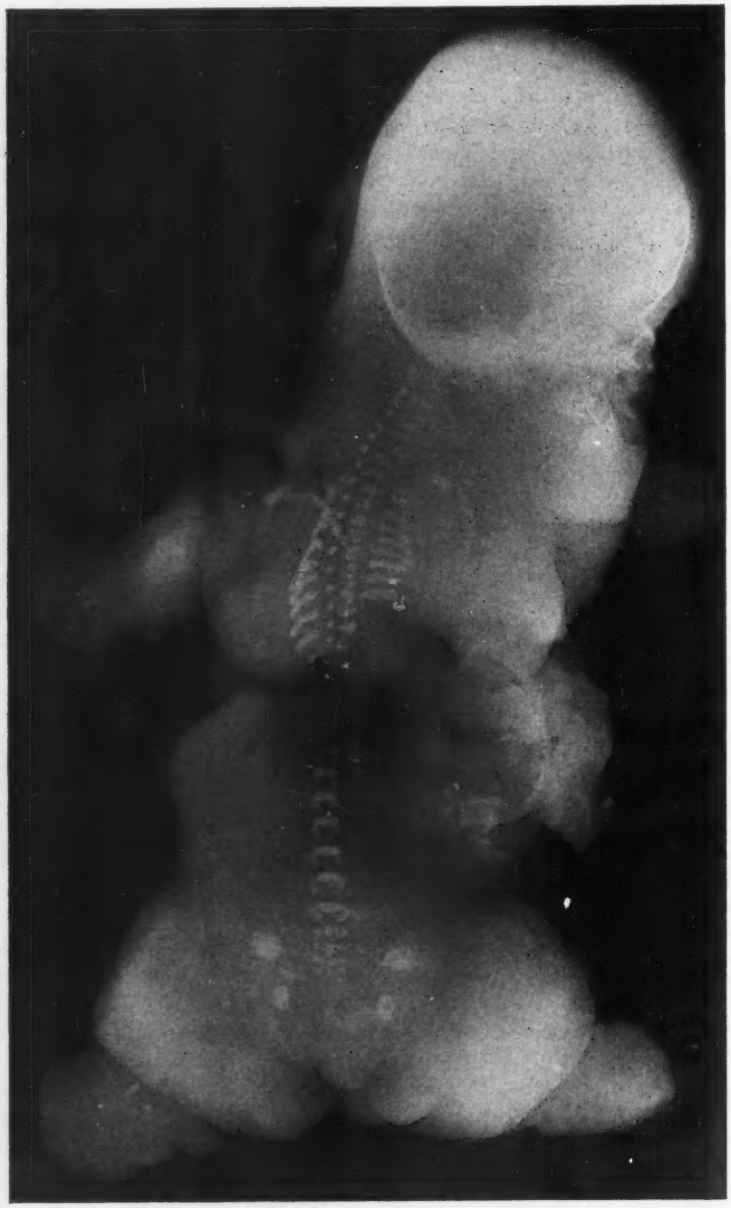

Fig. 2.—Extrauterine x-ray of the fetus.

Just subjacent to the level of the clavipectoral girdle three pairs of bilateral buds suggestive of rudimentary appendages were discernible. The right side was more developed than the left. There was a suggestion of three digits on one of the buds on the right side.

The anterior abdominal wall was absent in its upper portion, and viscera protruded. The site of the insertion of the cord could not be determined since the cord was detached during the delivery. In the region of the hypogastrium there was a mass of tissue, fleshy to palpation and appearing as a subcutaneous elevation.

The inferior appendages were foreshortened and proximally large. The legs were apparently absent bilaterally. The feet showed evidence of the heel being separate from the rest of the foot, and six rudimentary digits were visible on each foot. No bony tissue was palpable.

There was a persistent pilonidal sinus, and an anal orifice was in evidence. The urogenital area, however, appeared to be that of a female with rudimentary labia visible. The right side of the perineum was incompletely fused. It could not be definitely determined whether either a vaginal or urethral orifice was present. The continuity of the spine was interrupted as a result of the trauma of delivery.

No postmortem examination was performed because of excessive maceration.

Extrauterine X-ray of the Fetus (Fig. 2).—In the skull the parietal bones showed incomplete calcification. A broad and thickened nasal bone was present, and there was a large defect anteriorly in the mandible. Asymmetric broadening of the anterior portion of the left body fragment was evident.

In the cervical spine no significant changes were noted. An ossicle to the left of the cervical spine probably represented an ossification center in an accessory rudimentary appendage. The clavicles, present bilaterally, showed two irregular, elongated bone fragments overlying their outer aspects, the origin of which was not determined. Small ossicles representing the anlage of the scapulas were noted. The neck area presented a very marked soft tissue prominence, distorting the area grossly and extending over the cranium. Bilateral symmetric soft tissue masses were demonstrated, corresponding to the anterior inferior chest area.

The dorsal spine was mutilated inferiorly. The ribs were shortened and thickened; 11 ribs were noted on the right and 8 on the left. In the upper abdominal area there was an irregular soft tissue mass with extensive irregular deposits of bone, one of which simulated mandible formation.

There were no unusual findings in the lumbar spine or sacrum.

The lower extremities presented two pairs of calcified ossicle formations, the proximal group suggesting the anlage of the tibia and fibula. The distal group possibly represented the talus and calcaneus.

Comment

Specific etiological factors were lacking in the history of this case, except for the possible role of nutritional deficiency. A prolonged second stage of labor was caused by transverse lie and prolapsed upper extremities. Polyhydramnios had been diagnosed four months prior to the onset of labor. Delivery was accomplished by internal version and extraction by means of the Braun and Jardine hooks. Breech extraction in the usual manner was not possible because the anomalous lower extremities offered no hold for traction.

Summary

A rare case of congenital abnormality, phocomelus, is reported. The stillborn monster showed abnormal extremities, rudimentary digits, complete absence of the upper palate, and complete harelip.

We wish to express our appreciation to Dr. A. J. Bernstein, Director of Diagnostic Radiology, Bronx Hospital, for his evaluation of the x-rays in this case.

References

1. Gould's Medical Dictionary, ed. 5, Philadelphia, 1945, The Blakiston Company.
2. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, 1953, The Year Book Publishers, Inc., p. 483.

A CASE OF CRANIOSCHISIS WITH PLACENTAL ATTACHMENT TO THE DURA*

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CONGENITAL deformities and abnormalities occur in almost 1 per cent of newborn children. A child born with a deformity so pronounced that it interferes with the general or local development of the body is called a monster. Monsters often die in the early formative stage, but if delivered alive they usually succumb within a few hours or days, being incapable of extrauterine existence. There are two classes of monsters, single and composite, and three general varieties of single monsters are distinguished: (1) *monstra per defectum,* in which all or parts of an organ are missing; (2) *monstra per fabricam alienam,* in which an organ is wrongly formed or misplaced; and (3) *monstra per excessum,* in which an organ is enlarged or duplicated.

The case presented here belongs to the *monstra per defectum* variety of single monsters, in which amniotic adhesions connect parts of the fetus to the amnion and placenta.[1] These adhesions were formerly believed to be due to local inflammatory changes in the amnion which caused it to adhere to the parts of the fetus with which it came in contact. Such bands occasionally attach the head or a portion of the body to the amnion, but they are more often found between the ends of the fingers or toes and the amnion.[2, 3] The etiology is unknown, although there is no histologic evidence that the bands are inflammatory in nature.

Because of the interesting multiple anomalies, the following case is presented.

A 30-year-old woman (Bronx Hospital No. 284173), gravida iv, para iii, was admitted to the service of Dr. A. C. Posner on April 28, 1955, with a history of bright red vaginal bleeding and mild cramping pain. The last menstrual period was Aug. 21, 1954, and the expected date of confinement was May 28, 1955. The prenatal course had been uneventful. The blood pressure was 120/60, blood type 0, Rh negative, and Wassermann test negative; antibody titer studies were also negative. No rectal or vaginal examination was done. A blood transfusion was ordered.

X-ray pelvimetry showed a single fetus presenting as a breech with the back to the left and the head in the upper right quadrant. It was also noted that the base of the skull presented calcification changes, but the cranium as a whole was poorly defined and suggested some form of abnormality, possibly an associated acrania. The placenta appeared to be situated on the right and posteriorly and to extend down over the lower uterine segment, covering the os.

*Presented at a meeting of The Bronx Gynecological and Obstetrical Society, April 23, 1956.

Following transfusion of 500 c.c. of blood, the bleeding ceased, and the blood pressure and pulse were normal. On the following day, April 29, the patient had another episode of bright red vaginal hemorrhage. The blood pressure at this time was 120/70, and the fetal heart rate was 140 per minute. A blood transfusion was started, and sterile vaginal examination in the operating room under a double setup showed the cervix to be 2 cm. dilated with the placenta covering the internal os. The diagnosis was placenta previa centralis with bleeding. A low cervical two-flap cesarean section was performed. A living female infant with many congenital abnormalities was delivered from a double footing breech presentation.

The still living newborn infant was 44 cm. long and weighed 6 pounds, 6 ounces. The respiratory rate was 40 per minute with moderate infrasternal retraction with each inspiration. The heart rate was 166 per minute and regular with no murmurs. The skin was warm and slightly cyanotic.

Grossly the infant presented a number of congenital malformations, the most prominent of which were about the head and face. The membranes and the very edge of a discoid placenta were adherent to a fine, bluish, membranous structure covering the vertex in the midline. This membranous structure appeared to be dura. Palpation disclosed the absence of both parietal and frontal bones. There was an irregular disappearance of the superior portion of the temporal and occipital bones above a plane passing through the displaced eyes anteriorly to just above the normal-appearing external ears posteriorly. Hair-bearing skin covered the lateral portion of the head.

A 7 by 5 cm. pedunculated skin pouch extended laterally and anteriorly from the right frontal parietal area. The pouch did not appear to be related to the adherent membranes but instead appeared to be skin which would normally cover the vertex. At the distal end of this pouch were found numerous discrete, round, heaped-up, bluish-red mounds of tissue which resembled granulation tissue. These mounds averaged 1.5 cm. in diameter and did not bleed to the touch. Small blue eyes, two in number, were irregularly displaced to the right and left laterally. Just to the left of the midline of the face, at the level of the eyes, there was an oblique facial cleft which presented an oval orifice superiorly, through which could be seen what appeared to be meninges.

The left nostril was absent. An oblique right nostril contained a papillary projection in the midline of its external opening. The failure of proper fusion of the nasolateral with the nasomedial processes was further demonstrated by a bilateral cleft lip. The gingival border and the anterior palate were fused; however, the posterior portion of the palate was widely cleft.

The right thumb was absent, and the right wrist assumed a hyperflexed position. There was no resistance of the right wrist to passive motion. This absence of tone was even more marked than the generalized hypertonicity which this infant exhibited. A peculiar pedunculated, red, fingerlike structure without palpable bone content extended 2.5 cm. from the medial aspect of the right arm from a joint about 1 cm. above the olecranon.

There were no remarkable gross abnormalities of the left arm, back, chest, abdomen, rectum, female genitals, legs, or feet.

The infant lived for 36 hours and died at 1:50 A.M. on April 30, 1955. Necropsy confirmed the description, and the diagnosis included the following: (1) atresia of cranial bones with cranioschisis and craniomeningocele; (2) adherence of placental membrane to exposed dura; (3) persistent oblique facial cleft with displacement of eyes; (4) bilateral cleft lip and cleft palate; and (5) atresia of right thumb.

Summary

An interesting case of congenital abnormality is presented in which delivery by cesarean section was necessitated by placenta previa centralis associated with bleeding.

We wish to thank Dr. A. J. Bernstein, Director of Diagnostic Radiology, and Dr. H. Sckolnick, Department of Pathology, Bronx Hospital, for their kindness in cooperating in the study of this case. We also wish to thank Dr. William K. Hass for his assistance.

References

1. Greenhill, J. P.: Obstetrics, ed. 11, Philadelphia, 1955, W. B. Saunders Company, p. 584.
2. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, 1953, The Year Book Publishers, Inc., p. 45.
3. Lennen, C. G.: J. Obst. & Gynaec. Brit. Emp. 54: 830, 1948.

AN UNUSUALLY LARGE NONPATHOLOGICAL PLACENTA

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SINCE normal placentas weighing in excess of 1,000 grams are unusual we are reporting a nonpathological placenta that weighed 1,650 grams. Eastman[1] stated, "The normal full term placenta on an average weighs about one-sixth as much as the child, that is, about 500 grams . . . in syphilis the placenta may weigh one-fourth, one-third, or even one-half as much as the fetus. The largest placentas usually encountered are observed in cases of erythroblastosis of the fetus and placenta."

Levy[2] reported a number of cases in which the placenta exceeded 1,000 grams. This thesis by Levy in 1900 summarized fetal and placental weights in deliveries at the Clinique Baudeloque during the years 1896-1899. There were 374 fetuses that weighed over 4,000 grams in a total of 7,117 deliveries. The largest placenta in this series weighed 1,320 grams; the mother had polyhydramnios in which the amniotic fluid weighed 6,750 grams and the stillborn fetus weighed 4,270 grams. Other than the mention of the absence of syphilis, there were no additional clinical data. Levy cited larger placentas, one weighing 1,340 grams reported by Bustamente and one of 3 pounds and another of 6 pounds described by Stein. There is no reference identifying the latter's paper, however.

More recently placentas weighing 1,000 and 1,080 grams were reported by Magnin[3] and Riviere,[4] respectively. In each case the maternal serological test was negative and the fetus was Rh positive. Both fetuses died at birth, however, and the placentas were edematous.

Case Report

Mrs. L. McC., a 27-year-old white gravida iv, para iii, was at term on Sept. 17, 1955. She was first seen at the Obstetrical Clinic of the 3345th USAF Hospital, Chanute Air Force Base, Illinois, on April 11, 1955. Her weight was 130 pounds and blood pressure 120/72. The serological test for syphilis was negative and the blood type A, Rh positive.

The present prenatal course was complicated by two admissions with the diagnosis of mild pre-eclampsia. The first admission was on July 6, 1955, at 29 weeks' gestation because of a weight gain of 7¾ pounds during the preceding month, her normal weight being 115 pounds. The urinalysis was negative, the blood pressure 130/64, and there was no edema. The patient was discharged after three days' hospitalization with a satisfactory weight reduction.

On Sept. 1, 1955, an x-ray of the abdomen to rule out twins showed a single fetus. There was no radiological evidence of polyhydramnios.

She was again admitted on Sept. 7, 1955, at 38 weeks' gestation because of a 2 plus edema and 2 plus albuminuria. Her weight was 133½ pounds and the blood pressure 130/80,

Fig. 1.—Maternal surface of placenta. Ruler measures 18 cm.

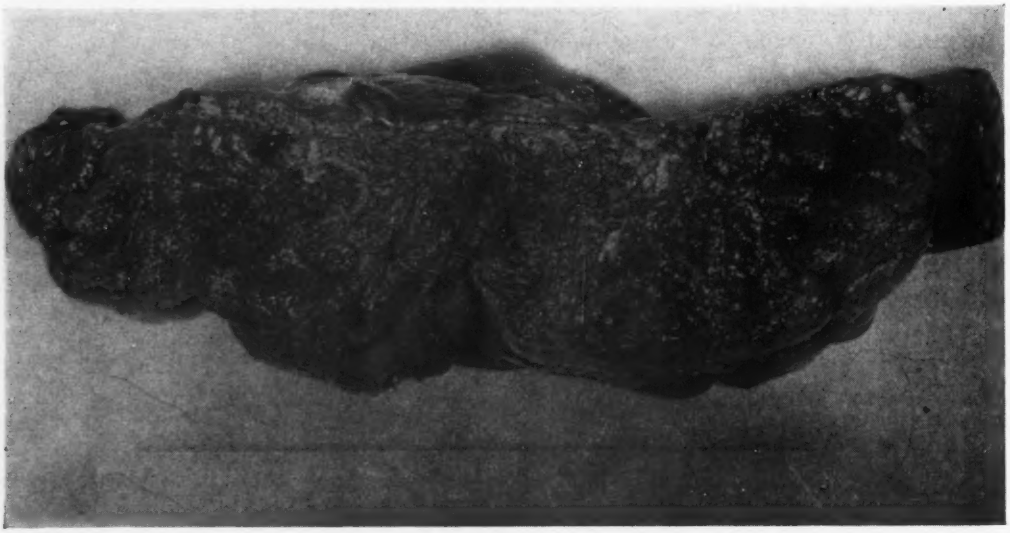

Fig. 2.—Cut surface of placenta.

this being the highest prenatal pressure. Again the patient responded well to the usual preeclampsia therapy.

On Sept. 13, 1955, while she was still hospitalized, labor started spontaneously and the patient had an essentially normal 9 hour and 10 minute labor. The membranes were ruptured in the delivery room and an estimated 400 c.c. of clear amniotic fluid was obtained. A 6 pound, 13 ounce male infant who breathed and cried immediately was delivered. As the uterus was larger than would have been expected in the third stage it was explored and the placenta and membranes were removed manually.

Figs. 1 and 2 show the placenta which measured 25 by 25 by 6 cm. and weighed 1,650 grams. It was grossly and microscopically normal.

The growth and development of the baby were normal when he was last seen on May 3, 1956, at the age of 7½ months. It is improbable that any blood group incompatibility could cause enlargement of the placenta without first having caused trouble with the baby.

Summary

A case of a nonpathological placenta that weighed 1,650 grams has been presented, with the elimination of erythroblastosis, syphilis, diabetes, and renal disease as contributing maternal conditions.

We wish to express our appreciation for the pathological report to Dr. Max Appel, Champaign, Illinois.

References

1. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc., p. 544.
2. Levy, Georges: Thèse de Paris, 1900.
3. Magnin, M.: Bull. Soc. gynéc. et obst., Lyon 1: 395, 1949.
4. Riviere, Chastrusse, and Boireau: Bull. Soc. gynéc. et obst., Bordeaux 1: 135, 1949.

732 N.W. 19TH AVENUE

A METHOD FOR DETERMINING THE PLASMA FIBRINOGEN TITER

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SEVERAL investigators have described procedures for estimating the fibrinogen content of plasma in recent years.[1, 2, 3] Some of these determinations indicate simply the presence or absence of a given fibrinogen level but not the tendency toward fibrinogenopenia. The method of Schneider[2] requires quick diluting at the bedside which may prove troublesome to attending physicians.

This paper describes an uncomplicated test for the detection of fibrinogen deficiency. Its merit in the diagnosis and management of acquired fibrinogenopenia will be discussed in a later paper. The technique is a modification of Schneider's[2] assay.

Plasma Fibrinogen Titer

Materials.—

13 by 100 mm. clotting tubes; 5 ml. and 1 ml. serologic pipettes.

Thrombin.* Dissolve the contents of one 50 unit vial in 0.5 ml. normal saline to yield a concentration of 10 thrombin units per 0.1 ml. Use fresh preparation only.

Normal saline, 0.85 per cent.

Patient's fresh plasma. Draw 5 ml. venous blood into a glass tube containing 19 per cent sodium citrate. Use 0.1 ml. 19 per cent citrate per 5 ml. blood. Centrifuge to obtain plasma.

Procedure.—

1. Arrange a series of 7 test tubes. Pipette no saline into the first tube, 4.5 ml. saline into the second tube, 0.5 ml. saline into the third tube, 2.0 ml. saline into the fourth tube, and 1.0 ml. saline into the fifth, sixth, and seventh tubes.

2. Place 0.5 ml. of the test plasma into the first and second tubes. With a fresh pipette mix the contents of the second tube by drawing up 6 times with pipette. Discard pipette.

3. With a fresh pipette, draw up 0.5 ml. of the plasma mixture in tube No. 2 and transfer it to tube No. 3. Also transfer an additional 0.5 ml. of the plasma mixture in tube No. 2 to tube No. 4. Mix the contents of tube No. 3 well, discarding pipette.

4. With a fresh pipette, mix the contents of tube No. 4 well, and draw up 1.0 ml. of the plasma mixture from tube No. 4, transferring it to tube No. 5. Mix well by drawing up in pipette, and in a similar way serially transfer 1.0 of the plasma dilution in tube No. 5 to tube No. 6, and 1.0 ml. of the plasma mixture from tube No. 6 to tube No. 7. Discard the final 1.0 ml. aspirated from tube No. 7.

5. At room temperature, add 0.1 ml. of thrombin solution to each tube. Mix well. Let stand for 90 seconds.

6. Read each tube by tilting gently in a horizontal position against a good light source. In tubes Nos. 1 and 2, a firm fibrin clot normally forms that adheres to the tube even with

*Fibrindex, Ortho Pharmaceutical Corporation, Raritan, N. J.

inversion. A transparent white pellicle forms in the remaining tubes. The highest dilution in which a visible single coagulum of fibrin is seen is the fibrinogen titer. When the end point is at 1:400 dilution (tube No. 7), the fibrin clot is small, filmy, and often adherent to the meniscus at the top of the plasma-saline mixture but can be observed with adequate inspection.

7. Tube dilutions are: No. 1, 1:1; No. 2, 1:10; No. 3, 1:20; No. 4, 1:50; No. 5, 1:100; No. 6, 1:200; No. 7, 1:400. A normal test with titer of 1:100 is illustrated in Fig. 1.

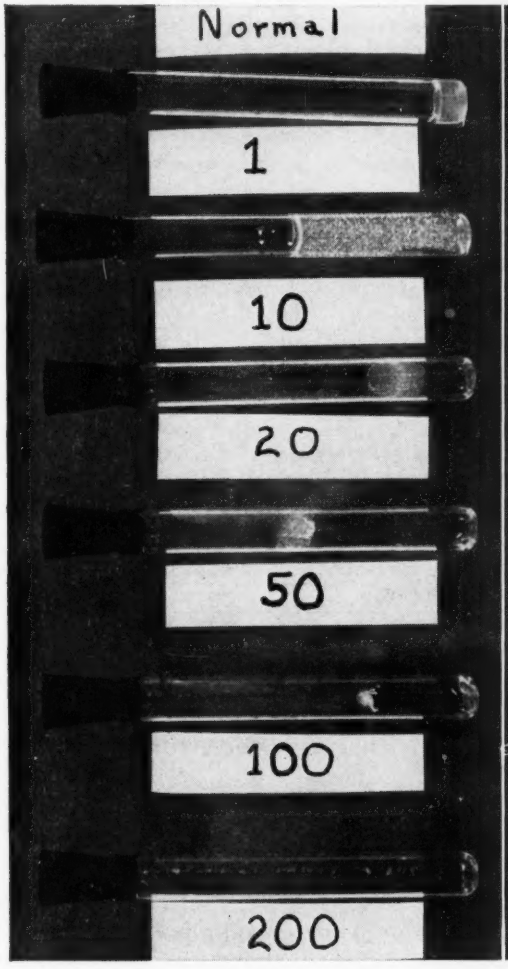

Fig. 1.

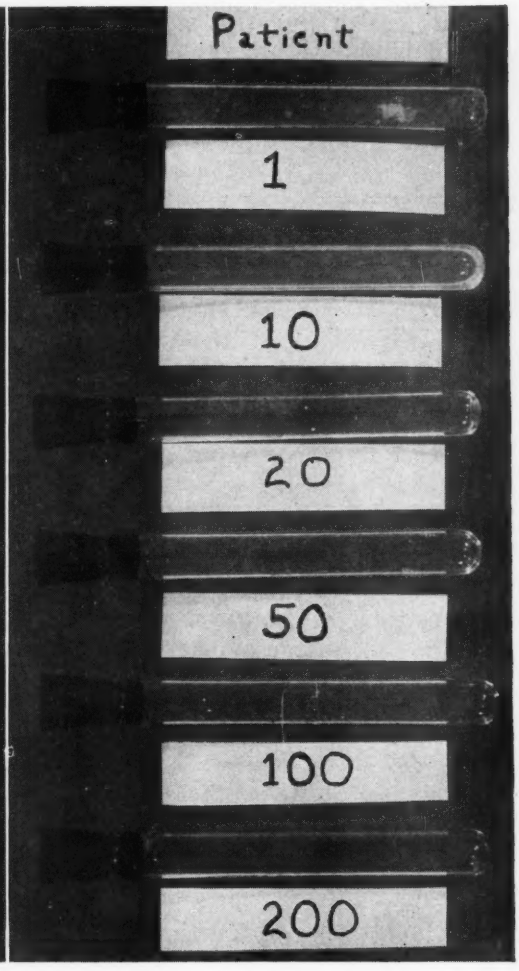

Fig. 2.

Fig. 1.—Normal plasma fibrinogen titer. (In dilutions 1 and 10 a solid fibrin clot adheres to the wall of the test tube. The end point is 1:100.)

Fig. 2.—Abnormal plasma fibrinogen titer in fibrinogenopenia. (In dilution 1 the weak fibrin clot is not adherent to the test tube. The end point is 1:1.)

To assess the normal parameters of the plasma fibrinogen titer, simultaneous quantitative plasma fibrinogen levels and titers (Table I) were obtained from plasma samples of 50 women in the thirty-sixth to the fortieth week of pregnancy, and in 15 normal, nonpregnant individuals. The quantitative plasma fibrinogen was assayed by the method of Ratnoff and Menzie,[4, a] with the use of a tyrosine calibration curve. In the former group, quantitative fibrinogen varied from 190 to 610 mg. per cent with a mean of 420 mg. per

cent, and the plasma fibrinogen titers from 1:100 to 1:400, with a mode* of 1:400. In normal, nonpregnant persons quantitative fibrinogen values fell within limits of 240 to 520 mg. per cent with a mean of 335 mg. per cent, and the plasma fibrinogen titer again measured from 1:100 to 1:400, with a mode* of 1:200. Although the fibrinogen titer represents a rough semiquantitative analysis, it was not possible to predict with accuracy the exact level of quantitative fibrinogen from the titer reading. A comparison between the fibrinogen titers and the quantitative fibrinogen present in the normal individuals comprising this study, and in two patients with acquired fibrinogenopenia is shown by Table II. In the 65 normal plasma samples, the mean fibrinogen value resulting in titers of 1:100 was 230 mg. per cent, in titers of 1:200 was 350 mg. per cent, and in titers of 1:400 was 450 mg. per cent.

TABLE I. SUMMARY OF FIBRINOGEN STUDY

		QUANTITATIVE FIBRINOGEN (MG. %)			FIBRINOGEN TITER*		
		VARIATION			VARIATION		
	NO. OF TESTS	LOWEST VALUE	HIGHEST VALUE	AVERAGE (MEAN)	LOWEST VALUE	HIGHEST VALUE	AVERAGE (MODE)
Normal pregnant	50	190	610	420	1:100	1:400	1:400
Normal nonpregnant	15	240	520	335	1:100	1:400	1:200

*The appearance of the normal titer test is illustrated by Fig. 1.

TABLE II. QUANTITATIVE FIBRINOGEN IN MILLIGRAMS PER CENT WITH RESPECTIVE FIBRINOGEN TITERS

ABNORMAL TITERS IN ACQUIRED FIBRINOGENOPENIA		NORMAL TITERS IN 65 NORMAL INDIVIDUALS						
		TITER 1:100		TITER 1:200		TITER 1:400		
TITER 1:1	TITER 1:20	NON-PREGNANT	PREGNANT	NON-PREGNANT	PREGNANT	NON-PREGNANT	PREGNANT	
15	35	250	190	275	365	485	540	610
		245		285	415	410	510	400
		240		280	280	520	595	430
				260	410	425	480	400
				340	390		545	395
				360	370		400	415
				330	340		420	450
				320	405		585	420
					290		450	420
					410		440	415
					350		405	420
					405		485	425
					395		470	450
					400		390	400
					390		395	410
					350		410	440
								410
Mean quantitative fibrinogen		230		350		450		

Comment

The fibrinogen estimation test outlined by Schneider[2] uses whole blood in lieu of plasma. Simultaneous determination of a normal control is recommended which is not always available. The titer of the test case and the specimen from a normal pregnancy are contrasted to see if an abnormal value and

*Mode, the measurement representing the greatest number of observations.

fibrinogen deficiency are the result. The fibrinogen titer described above consumes a minimum of time, and is done in the laboratory by the technician accustomed to quick and accurate preparation of plasma dilutions. No search for a control is necessary, as study involving 65 normal patients (Table I) has served to establish the usual limits of this procedure.

The titer was found identical in the fasting and the nonfasting states. The end point may diminish if a thrombin concentration of less than 10 units is added to each plasma dilution, but the titer is not increased by furnishing more than 10 thrombin units to each tube. Since the conversion of fibrinogen to fibrin in the test plasma is effected by the thrombin supplied to the system and not by natural thrombin evolution in that plasma, calcium is not required for the reaction. Thus a diluent of Ringer's solution containing 0.02 M calcium or of normal saline will result in similar fibrinogen titers. Use of 19 per cent sodium citrate results in minimal dilution of the plasma fibrinogen content from the added anticoagulant, as a 97 per cent plasma concentration is customarily obtained from the small amount of citrate in the plasma mixture.[4, b] By contrast, use of 0.1 M sodium oxalate and other anticoagulants yields only an 83 per cent plasma concentration which artificially dilutes the patient's plasma fibrinogen prior to testing.

Although quantitative plasma fibrinogen is always the preferred measurement, the assay is lengthy and its infrequent performance in most laboratories may limit its accuracy when it is urgently needed in an instance of obstetrical hemorrhage. The plasma fibrinogen titer has the advantage of rapidity in informing the physician whether adequate fibrinogen is present, and of the precision offered by a semiquantitative estimate with known controls. Serial determinations, similar to an Rh antibody titration, also can be employed in any pregnancy, particularly when intrauterine fetal death ensues. A fall in titer, especially below levels of 1:100 dilution, may herald gradual defibrinogenation of the maternal blood and anticipate a hemorrhagic state. An abnormal fibrinogen titer obtained from a case of acquired fibrinogenopenia is represented by Fig. 2.

Summary

A modified plasma fibrinogen titer has been devised which is useful in the early diagnosis of fibrinogenopenia.

I am indebted to Dr. H. O. Singher of the Ortho Research Foundation, Raritan, New Jersey, for providing the thrombin (Fibrindex) used in establishing normal values of the plasma fibrinogen titer.

References

1. Bonsnes, R. W., Sweeney, W. J., III: Am. J. Obst. & Gynec. 70: 334, 1955.
2. Schneider, C. L.: Am. J. Obst. & Gynec. 64: 141, 1952.
3. Weiner, A. E., Reid, D. E., and Roby, C.: Am. J. Obst. & Gynec. 66: 475, 1953.
4. Tocantins, L. M.: The Coagulation of Blood. Methods of Study, New York, 1955, Grune and Stratton; a, p. 155; b, p. 12.

DOES RETROPLACENTAL HEMATOMA CONTAIN FETAL BLOOD?

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RETROPLACENTAL hematoma is formed by the blood insinuating itself between the separating placenta and the remaining decidua basalis. The purpose of this investigation was to establish whether this hematoma is constituted exclusively of maternal blood, or of blood of both maternal and fetal origin. The concentration of fetal hemoglobin in the retroplacental hematoma was therefore determined and compared with that in the maternal and in the umbilical cord blood.

Method

In a series of 41 normal deliveries the fetal hemoglobin per cent concentration of the retroplacental hematoma was measured. In all these cases the hematoma was demonstrable within the inverted sac of the placenta. Fetal hemoglobin per cent concentration was also determined in the venous blood of the mother and in the umbilical cord blood. Determination of fetal hemoglobin per cent concentration was performed in clotted blood according to the method described by Singer and Chernoff.[1]

The per cent of fetal blood present in the retroplacental hematoma was calculated according to the following formula:

$$\text{Fetal blood \% in hematoma} = \frac{\text{Maternal Hb. in Gm./100 c.c. (Retroplacental Fetal Hb.\% - Maternal Fetal Hb.\%)}}{\text{(Umbilical Fetal Hb.\% - Retroplacental Fetal Hb.\%) Umbilical Hb. in Gm./100 c.c.}}$$

Results

In all cases examined, fetal hemoglobin per cent concentration was significantly higher in the retroplacental hematoma than in the maternal venous blood and ranged from 0.7 per cent up to 3.8 per cent.

The differences between the fetal hemoglobin per cent concentration in retroplacental and maternal blood ranged between 0.3 per cent to 1.9 per cent (Table I).

The fetal hemoglobin per cent concentration in the cord blood varied from 75 per cent to 95 per cent in agreement with the results of other authors.[2]

The portion of the retroplacental hematoma composed of fetal blood as calculated by the above formula was from 0.18 per cent to 1.33 per cent of the total blood in the hematoma.

Comment

The results obtained in this study appear to demonstrate that minimal amounts of fetal blood occur in the retroplacental hematoma. This suggests that during the course of separation of the placenta some damage to the villi

TABLE I. CONCENTRATION OF FETAL BLOOD IN RETROPLACENTAL HEMATOMA

CASE NUMBER	FETAL Hb.% CONCENTRATION IN CORD BLOOD	FETAL Hb.% CONCENTRATION IN MATERNAL BLOOD	FETAL Hb.% CONCENTRATION IN PLACENTAL HEMATOMA	TOTAL Hb. CONCENTRATION IN GM./100 C.C. IN THE MOTHER	TOTAL Hb. CONCENTRATION IN GM./100 C.C. IN CORD BLOOD	% OF RETROPLACENTAL BLOOD OF FETAL ORIGIN
1	79.0	0.4	0.7	9.5	20.0	0.18
2	89.0	1.8	2.1	11.5	18.0	0.22
3	90.0	2.4	2.8	11.0	21.5	0.25
4	87.0	2.0	2.5	8.5	17.0	0.30
5	80.0	1.7	2.2	10.3	19.5	0.33
6	80.0	1.3	1.9	9.0	20.0	0.35
7	92.0	1.7	2.4	9.8	21.0	0.36
8	83.0	2.2	2.7	10.5	17.0	0.38
9	82.0	1.5	2.1	10.2	20.0	0.39
10	94.0	1.1	1.8	9.8	18.0	0.41
11	91.0	2.1	2.9	9.5	19.5	0.44
12	87.0	1.6	2.3	10.5	19.7	0.45
13	79.5	1.8	2.5	10.5	17.5	0.50
14	79.0	1.5	2.3	9.0	17.5	0.54
15	82.0	1.7	2.4	11.0	17.0	0.57
16	93.0	0.9	1.8	11.0	18.5	0.58
17	85.0	0.7	1.8	8.5	19.5	0.58
18	95.0	1.0	2.0	11.2	20.5	0.58
19	92.0	1.4	2.5	9.6	19.0	0.62
20	84.0	2.3	3.2	10.5	18.5	0.63
21	90.0	1.5	2.4	11.5	18.0	0.65
22	81.0	1.2	2.1	11.5	20.0	0.66
23	79.5	0.4	1.7	8.0	19.0	0.70
24	88.0	1.0	2.1	10.5	19.0	0.70
25	81.0	0.8	1.8	10.5	18.5	0.73
26	80.0	1.1	2.3	10.8	21.0	0.79
27	92.0	1.8	2.9	11.2	17.5	0.79
28	91.0	1.0	2.3	10.0	18.0	0.80
29	87.0	0.9	2.4	10.0	22.0	0.80
30	92.5	0.9	2.5	9.2	20.5	0.80
31	92.0	2.0	2.5	10.8	7.5	0.80
32	91.0	1.9	3.0	10.8	17.0	0.80
33	81.0	1.7	3.0	10.0	19.5	0.87
34	88.0	1.9	2.7	11.0	21.0	0.88
35	91.0	1.2	2.7	11.2	21.0	0.90
36	83.0	0.8	2.3	9.2	18.5	0.92
37	80.0	0.8	1.9	10.8	16.5	0.92
38	91.0	0.9	2.8	9.2	21.0	0.94
39	83.0	0.9	2.2	12.0	20.0	0.96
40	91.0	0.5	2.4	9.3	17.5	1.10
41	75.0	1.9	3.8	10.5	21.0	1.33
Mean		1.4	2.4			
Standard deviation		±0.53	±0.5			
Standard error		±0.081	±0.077			
Range		2.0	3.1			

Critical ratio t test $= \frac{2.4 - 1.4}{0.11} = 9.0$

may occur even under physiological conditions. It therefore appears possible that between the expulsion of the fetus and that of the placenta, retroplacental blood containing some fetal red cells is forced into the maternal sinuses of the contracting uterus.

This observation confirms the hypothesis suggested by Potter[3] that immunization of the mother by fetal blood is due to the entrance of fetal cells into the maternal circulation not only during the course of pregnancy, but chiefly at the time of delivery. This hypothesis was advanced to explain the

finding that the concentration of antibodies almost always increases during the weeks following delivery when it may reach several times the maximum levels during pregnancy.[4]

It is assumed[5] that 0.0672 c.c. of packed Rh-positive red blood cells is required to immunize an Rh-negative mother. According to our data such a quantity of fetal red blood cells is contained in about 10 c.c. to 70 c.c. of retroplacental blood.

It appears, therefore, that isoimmunization of the mother in cases of fetomaternal incompatibility may depend on the possible entrance of a large amount of retroplacental blood into the maternal circulation. The relatively low incidence of maternal blood sensitization may be explained by assuming that only occasionally does the full amount necessary for immunization enter the maternal circulation.

The question arises whether retroplacental hematoma due to premature separation of the placenta may also induce isoimmunization in cases of fetomaternal incompatibility.

It is possible that, in such circumstances as well, fetal blood may enter the maternal circulation, since in a case of premature separation of the placenta we found unusually high levels of fetal hemoglobin in the maternal circulation.

Summary and Conclusions

In a series of 41 cases of normal delivery the retroplacental hematoma showed a fetal hemoglobin per cent concentration of from 1.8 per cent to 3.8 per cent, significantly higher than that in the maternal venous blood; the differences ranged from 0.3 per cent to 1.9 per cent. This difference indicates that the retroplacental hematoma is composed of fetal blood to the extent of from 0.18 per cent to 1.33 per cent of the amount of blood in the hematoma.

It is suggested that in fetomaternal blood incompatibility, maternal immunization is enhanced by the entrance into the maternal circulation of fetal erythrocytes contained in the retroplacental blood.

References

1. Singer, K., Chernoff, A. I., and Singer, L.: Blood 6: 413, 1951.
2. Walker, J., and Turnbull, E. P.: Arch. Dis. Childhood 30: 111, 1955.
3. Potter, E. L.: Rh: Its Relation to Congenital Hemolytic Disease, Chicago, 1947, The Yearbook Publishers, Inc.
4. Potter, E. L.,[3] p. 46.
5. Levine, P.: Am. J. Obst. & Gynec. 42: 165, 1941.

POLYCYTHEMIA ASSOCIATED WITH UTERINE MYOMAS

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(From the Holzer Hospital and Clinic)

WITHIN the past three years there have been reported 3 instances of polycythemia with apparent cure following hysterectomy for myomas. Thomson and Marson[1] reported the first such case in 1953, and stated that the blood picture was still normal twenty-two months after operation. Horwitz and McKelway,[2] in reporting their case, suggested that arteriovenous shunts within the tumor might induce a polycythemic response. These authors analyzed the records of 9 women with polycythemia and found that 2 had myomas. There was disappearance of the polycythemia and maintenance of a normal blood picture for eight years following hysterectomy in one case, but the second showed no change. The first mentioned case is the basis for their report. Engel and Singer[3] indicated that their patient had maintained normal blood values for six months following operation.

The records of 7 cases of polycythemia in females taken from files of the Holzer Hospital have been reviewed. One, reported below, seems to constitute the fourth reported instance of apparent cure of polycythemia following hysterectomy for myomas.

Case Report

A 29-year-old white woman, para 0, gravida 0, was first seen on Nov. 19, 1954, with the chief complaint of pain in the right side of the abdomen, present for about three months with increasing severity. Her periods had been normal and unchanging. There had been a single episode of slight vaginal bleeding following examination by her family physician. The abdominal pain seemed intensified shortly prior to the menstrual periods. The history failed to disclose symptoms suggestive of polycythemia.

The physical examination showed a slight facial flush with circumoral pallor. The conjunctivae were suffused and the vessels were prominent. The retinal veins seemed distended. Examination of the ears, nose, mouth, heart, and lungs was negative. The examination of the abdomen revealed a large, firm-to-semisolid, nontender mass rising out of the pelvis, extending 2 cm. above the umbilicus. The size limited the mobility of this mass. Pelvic examination confirmed the pelvic origin of the mass. Visualization of the cervix was not possible because of the distortion induced by the mass. Rectal examination failed to reveal any intrinsic rectal lesions. There was no apparent splenomegaly.

The chest x-ray was normal except for some elevation of both diaphragms. Flat plate of the abdomen showed only a large mass without calcification or fetal parts. The urinalysis was normal. The red blood cell count was 7.5 million per cubic millimeter, the hemoglobin 19.2 Gm. per cent, the hematocrit 64 per cent, the white blood cell count 9,850 per cubic millimeter with a normal differential. The platelet count was 230,000 per cubic millimeter. The total blood volume was 8,779 c.c. with a plasma volume of 3,424 c.c. (Evans blue dye method). The expected normals were 5,525 c.c. blood volume and 2,995 c.c. plasma volume. Bone marrow aspiration was done. The marrow was interpreted as demonstrating an erythroid

hyperplasia. The hyperplasia was orderly, and there was no significant increase in immature elements. Myeloid components were normal and megakaryocytes were abundant.

Removal of the presumed myomatous uterus was delayed pending control of the polycythemia. Over a fourteen-day period 2,000 c.c. of blood was removed in 500 c.c. amounts. On the day prior to hysterectomy, the red blood cell count was 5.1 million, the hemoglobin 13.7 Gm., the hematocrit 46 per cent, the total blood volume 6.887 c.c., and the plasma volume 3,846 c.c. The white blood cell and differential counts were again normal.

On Jan. 5, 1955, pelvic laparotomy was performed. Examination showed a large, firm-to-semisolid tumor mass arising deep in the cul-de-sac, pressing the uterus and adnexa forward. A total hysterectomy with bilateral salpingo-oophorectomy was necessary. The specimen weighed 14 pounds (6.4 kilograms) and measured 31 by 28 by 12.5 cm. Large vascular channels up to 1 cm. in diameter were frequently encountered. The microscopic examination showed a pattern typical of a leiomyoma except that there were areas of severe interstitial edema. The bands of smooth muscle fibers were separated by pseudocystic spaces containing fluid. Intrinsic vascular channels were dilated and had thickened, sclerotic walls. These changes have been observed in other uterine leiomyomas, particularly large ones in positions causing impairment of vascular drainage or blood supply. In this specimen, the large leiomyoma was arising in the posterior cervical segment and had been impacted in the pelvis and lower abdomen. Verhoeff's elastic stains and periodic acid-Schiff stains were done on numerous sections in an attempt to demonstrate an anomalous vascular pattern, but none was present.

The postoperative course was uncomplicated, and the patient was discharged on the sixth postoperative day. The following chart summarizes hematological data obtained since the operation on Jan. 5, 1955.

	RED BLOOD COUNT	HEMOGLOBIN	HEMATOCRIT	BLOOD VOLUME	PLASMA VOLUME
2/ 5/55	4.10 million	12.2 Gm.	38%		
3/19/55	4.80 million	13.0 Gm.	42%		
9/26/55	4.00 million	12.0 Gm.	40%		
1/ 4/56			40%	4,620 c.c.	2,865 c.c.
5/ 9/56			41%		

Comment

The unusual occurrence of polycythemia apparently cured by removal of coexisting myomas as yet remains unexplained. Certainly, the physical examination, hematological examination, and the response to surgery are unlike those in polycythemia vera (erythremia). Diseases of the cardiopulmonary system capable of producing anoxemia and a secondary polycythemia (erythrocytosis) were not present. The criteria necessary for establishing the diagnosis of Cushing's syndrome were not met. The patient had not taken drugs, such as cobalt, capable of inducing an abnormal rise in the red blood cell count. The suggestion made by one author that arteriovenous shunts within the tumor bring about the polycythemia does not seem tenable. Intracardiac shunts with flow of unoxygenated blood into the systemic circulation will induce polycythemia as a result of tissue anoxia. Similarly, pulmonary arteriovenous fistulas produce polycythemia by the same stimulus of anoxia. However, peripheral arteriovenous fistulas produce only a rise in the total blood volume rather than an elevation limited to red cell mass. The relationship between the two manifestations (polycythemia and myomas) remains clouded.

We suggest the brief and descriptive term "myomatous polycythemia" to identify this syndrome. The following criteria are suggested for establishing the diagnosis: (1) polycythemia (increased red blood cell mass); (2) myomatous uterus; (3) restoration of normal hematological values following hysterectomy alone, or failure of the polycythemia to reappear following hysterectomy alone.

Summary

The fourth recorded instance of polycythemia with myomas, apparently cured by hysterectomy, is reported. Criteria for establishing this diagnosis are presented. The term "myomatous polycythemia" is suggested to identify this syndrome.

References

1. Thomson, A. P., and Marson, F. B. W.: Lancet 2: 759, 1953.
2. Horwitz, A., and McKelway, W. P.: J. A. M. A. 158: 1360, 1955.
3. Engel, H. W., and Singer, K.: J. A. M. A. 159: 190, 1955.

CLINICAL NOTE ON THE USE OF INTRAVAGINAL TAMPONS DURING MENSTRUATION

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MANY women who prefer to use a vaginal tampon, rather than a pad, as protection during menstruation often regret not being able to do so because of abundant flow the first day or two. Many businesswomen prefer tampons for various reasons and are sorry when they are not able to use them. This report is based on results of a suggestion first made several years ago to 25 women patients that they douche in the morning to wash out the overnight accumulation of menstrual flow in the vagina before inserting the tampon. The idea was that it would then be possible to use a tampon with safety because the amount of flow following the douche would be much less profuse.

The Douche Procedure.—The bulb type douche syringe is recommended because it is most efficient, convenient, quick, and easy to use. The best type of douche syringe is the "whirling spray." Three or four tablespoonfuls of distilled (white or artificial) vinegar to a quart of warm water is recommended as the douche solution. The tampon is inserted immediately on completion of the douche.

Results.—These women have reported they are now able to use the tampon even on days of greatest menstrual flow. Much greater use of the intravaginal tampon is possible when the morning douche is taken.

Comment by Patients.—Most women are amazed by the suggestion that a douche be taken during menstruation. All who have been persuaded to try it, continue to do so. No discomfort or ill effect of any nature has been reported or detected by vaginal examination as a result of douching with a warm vinegar solution daily while menstruating.

A frequent comment is that not as much menstrual flow was noted. A few women suspected the douche "stopped" the flow. It was made clear to them that all the morning douche can accomplish is to wash out the menstrual discharge which has accumulated in the vagina overnight. It is not possible for a douche to change or interfere with the total amount of material expelled from the uterus because that is determined by the action of the ovarian hormones on the endometrial lining of the uterus since the previous menstrual flow. Nor is the douche solution able to pass through the cervical canal into the uterus to "wash out" the uterus—as some women suppose. Any physician who has performed a tubal patency test can testify about the difficulty sometimes encountered in introducing air or oil into the uterus.

Any physician knows there is a steady, slow rate of endometrial slough which collects in the vagina overnight. The apparent abundant morning flow is nothing more than this material accumulated in the vagina being expelled on rising. Lying or erect, there is little change in the rate of discharge from the uterus.

The Vinegar Douche Solution.—In my experience, the clinical safety of using vinegar douches during menstruation has been completely adequate,

whether or not the tampon has been impregnated with an acid buffer. No concern need be felt about the possible introduction of pathogens when inserting the tampon. Only a plain water, saline, or alkaline douche is contraindicated.

Distilled vinegar (white or artificial) has a 5 per cent acetic acid strength. When 1 to 4 tablespoonfuls of 5 per cent vinegar is added to one quart of warm water, a douche solution with acidity of pH 4.15 to 3.54 is obtained.

f℥ ss	to 1 quart of tap water	pH 4.15
f℥ i	1 quart	3.70
f℥ iss	1 quart	3.60
f℥ ii	1 quart	3.54

Thus 3 or 4 tablespoonfuls of 5 per cent vinegar to 1 quart of warm water makes an ideal douche solution from the viewpoint of the pH value. Its cleansing effect is efficient, judged by examination of many women these past fifteen years. Such a douche solution will neutralize any existing alkalinity (such as blood or pathological discharges) and leave the vaginal acidity within normal range. Should vaginal acidity be in excess of pH 3.5, the vagina is thoroughly cleansed and the residual pH is of optimal strength to encourage growth of the Döderlein bacilli. There is probably no other physiological douche solution universally available, inexpensive, and more efficient than the simple vinegar-in-water solution for routine use. Using four or more tablespoonfuls of vinegar to a quart of warm water, an excellent spermicidal solution is obtained which can be confidently used as a contraceptive procedure.

The Effect of the Vinegar Douche During Menstruation on the Normal Vagina in the Absence of Infection.—The vinegar douche increases vaginal pH, which effect in turn encourages the growth of the Döderlein bacilli; because of the accompanying cleansing effect of the vinegar water which splashes the labia and perineum, the introduction of the vaginal menstrual tampon is actually made safer.

The Effect of the Vinegar Douche During Menstruation on the Vagina When Cervical Infections and Vaginal Discharges Are Present.—For many years I have prescribed a morning vinegar douche daily during menstruation for women undergoing treatment for endocervicitis, Trichomonas vaginitis, and fungus vaginitis. In addition to all the benefits derived when no vaginal or cervical infection is present, the vinegar douche also prevents the menstrual flow from acting as a culture medium for the growth of infecting bacteria, protozoa, or fungi. No ill effects have ever been noted in hundreds of women over fifteen years. Indeed, in my experience, use of the vinegar douche during menstruation proved to be a valuable prophylactic as well as therapeutic procedure. Incidentally, since the tampon prevents irritating vaginal discharges from coming in contact with the vulva and perineum, much irritation and discomfort are prevented.

The Intravaginal Menstrual Tampon Is Safe to Use.—One of the widely used brands of intravaginal tampons is adjusted to a pH comfortably on the acid side.[1] This is, in my opinion, adequate to inhibit the growth of any bacteria inadvertently introduced during the insertion of the tampon, with or without prior vinegar douching, provided only that perineal cleanliness is fair.

Frequent change of the tampon during the day, with or without repeating the vinegar douche, also encourages the maintenance of a normal vaginal pH. So far as danger of introducing infection is concerned, use of the acid-buffered intravaginal tampon actually tends to decrease the likelihood of cervical or vaginal infection.

A possible reason some women state the intravaginal tampon is inadequate the first day may be because many women do not believe such a small piece of cotton can possibly absorb what they consider to be a "tremendous" loss of blood. Another thing that contributes to this belief, when failure of protection actually happens, is that, because of the fact that the tampon is so comfortable and is actually unnoticed in use, they forget to change the tampon, and the length of time between changes is apt to be much longer than when an external pad is used.

External pads are rarely changed because they have reached their absorptive limit, but rather because they are uncomfortable and odorous. Since the intravaginal tampon is neither uncomfortable nor odorous, there is a definite and real tendency to change less frequently. The mistaken impression that the tampon does not offer adequate protection may, therefore, be due only to infrequent change the first day or two. The morning douche is of real value during the "peak" day or two of flow: less frequent change will be necessary the remainder of the day.

Summary

The "normal" woman, whose hormone balance is adequate to maintain a vaginal pH of 3.5 to 5.0 and abundant Döderlein bacillus vaginal flora, need only use a vinegar douche *during* menstruation to overcome the undesired alkalinizing effect of the menstrual flow.

When a cervical or vaginal infection is present, use of a vinegar douche in the morning during the menses actually tends to prevent a flare-up of the infection, and is, therefore, a valuable prophylactic, as well as therapeutic, adjunct to treatment.

Those girls and women who prefer to use vaginal tampons during menstruation, but who have been unable to do so because of a profuse amount of flow, have been advised to douche in the morning and use the tampon. By washing out the overnight accumulation of menstrual flow, there is much less apparent flow and the tampon is adequate protection. Two tampons can be inserted if desired.

No ill effects on menstruation or pelvic organs have yet been complained of, or noted on examination, by girls and women who have used a vinegar douche daily while menstruating. In my opinion, it is impossible to speculate upon what ill effects could possibly follow such a procedure.

The intravaginal menstrual tampon is safe to use whether or not cervical or vaginal infection is present.

Every woman who has accepted the suggestion to use the warm vinegar water douche solution and vaginal tampons while menstruating has been delighted with results.

Physicians can confidently recommend the use of intravaginal menstrual tampons because they are comfortable, adequate, and safe to use. Also because they eliminate the inexpedient contact between anus and vulva which the external pads afford, use of menstrual tampons should be actively urged.

Reference

1. Personal communication from Tampax, Incorporated.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Doctor and Patient and the Law. By Louis J. Regan. Third edition, 716 pages. St. Louis, 1956, The C. V. Mosby Company. $12.50.

In recent years the medical profession has been beset by increasing claims arising from alleged malpractice. In many instances, the basis of these suits is the result of the physician's failure either to comprehend or to give due consideration to the medical-legal requirements in the practice of medicine. In *Doctor and Patient and the Law* Dr. Regan not only defines the terms associated with malpractice, but amply illustrates by case presentations many of the aspects of this branch of the law. He outlines, in considerable detail, the important aspects of the physician-patient relationship, including discussion of consents for operations, invasion of the right of privacy, and privileged communication. Of particular importance to the physician is the adequate portrayal of the role of the doctor as a witness in a court of law. This book includes a very complete chapter devoted to such items of importance to the obstetrician and gynecologist as: abortion, adoption, artificial insemination, and contraception statutes. One of the most interesting sections of this comprehensive volume is that related to the "malpractice prophylaxis." In this area Dr. Regan indicates the importance of records, hazardous therapy, liability for acts of another, insufficient treatment, and unethical criticism of a professional colleague.

Les Méthodes psychosomatiques d'accouchement sans douleur. By L. Chertok, 268 pages. Paris, 1957, L'Expension Scientific Française.

Written by a psychiatrist, this is an extensive scientific survey of psychosomatic treatment of pain in childbirth. The author objectively presents the historical, theoretical, and clinical aspects of this field.

The book offers a review of the evolution of the hypnosuggestive concept and its relationship to delivery. The Read method, the psychoprophylactic method of the Soviet Union (Velvoski method), and the variation of these methods are fully described.

The controversial and insufficient theoretical bases for these methods are clearly presented. The lack of scientific knowledge in regard to pain in childbirth, and the lack of criteria for the measurement of pain are well taken into account.

The combination of the didactic, physiotherapeutic, and psychotherapeutic elements, common to both and Read and Velvoski methods, is shown, with documentation, to be effective as analgesia in childbirth. The medical and psychosocial implications of the psychosomatic approach to delivery are indicated.

Endocrinologia de la mujer. By Jose Botella Llusia. Second edition, 780 pages, 660 figures. Barcelona, 1956, Editorial Cientifico Medica.

A most extensive work in the field of female endocrinology, this book consists of forty chapters arranged in ten major sections. The author opens the book with an introductory chapter followed by sections on: the sex hormones, extragonadal factors which govern sexuality, the sexual cycle, the evolution of sex, pregnancy, labor, and puerperium, endocrine syndromes with effects on sex, pathology of the evolution of sex, endocrinological investigation of a patient, ovarian syndromes, endocrinological pathology of pregnancy, and an appendix on the endocrine basis of genital tumorigenesis. As can be seen from the above titles, the entire subject is covered in an orderly manner. The exposition of each subject is logical, concise, and well documented. There is a large bibliography at the end of each chapter. The colored reproductions are technically poor. There are many excellent diagrams to illustrate the text.

The Queen Charlotte's Text-Book of Obstetrics. Edited by G. F. Gibberd et al. Ninth edition, 547 pages, 246 illustrations. Boston, 1957, Little, Brown & Company. $11.50.

Queen Charlotte's Maternity Hospital is the oldest lying-in hospital in the British Isles, dating back to 1739. Needless to say, many British obstetrical mores find origin in this center. This book, written by eight practicing obstetrical specialists and seven consultants, is a continuation of a practical textbook of obstetric techniques common to the British Isles.

American obstetricians will be interested in the British approach to obstetrical problems, and this text highlights certain differences in practice between our countries. There it is still common for women to have home confinements, although the custom is gradually being superseded by hospital delivery. All management takes this fact into account. The use of "flying squads" in emergencies is common and the necessity for such techniques as bipolar version (Braxton Hicks version) in partial placenta previa, and internal version (internal podalic version) in shoulder presentations is still mentioned. Since cesarean section cannot safely be performed under home conditions, techniques not generally in use in the United States are still apparently practiced, although the text makes the reader aware of the high perinatal loss associated with these procedures.

Simulation with oxytocics and rupture of the membranes are adequately discussed, but such procedures as the use of the Drew-Smythe catheter for high rupture of the membranes and metal dilators for the closed external os are still suggested. Because of the differences in obstetric practice in the United States and Great Britain, medical students may find this text at considerable variance with accepted practice here.

It is a distinct disappointment to this reader to find that the literary style so much admired in other British texts is absent in this important one.

Neonatal Surgery. By Peter Paul Rickham. The Commonwealth Fund. 93 pages. Boston, 1957, Harvard University Press.

The detailed results of painstakingly thorough metabolic studies in 9 neonatal surgical patients are presented. The studies are analyzed in detail and discussed against a background of the literature on similar studies in adults and older children.

The book should be of the greatest interest to pediatricians and pediatric surgeons. Clinical studies in 9 cases which are each unlike the other do not form a basis for a final assessment of the metabolic problems involved. There does appear to be some consistent difference between the responses of newborn infants to surgery and the responses of children more than 2 or 3 weeks old. The most obvious difference is in the potassium metabolism, the newborn infants losing no more potassium than can be accounted for by their starvation, and apparently losing little or no potassium as the result of the trauma of the particular operations studied.

In some patients rather large sodium shifts appeared to take place rather suddenly. In many instances in the face of positive nitrogen and sodium balances there was little or no gain in weight. The enormous difficulties in total specimen collection in infants and measurement of fluids regurgitated, spat out, etc., even in such meticulous studies as these, give rise to substantial opportunities for significant error.

There is a brief and simple chapter on practical applications. Notable are the deliberate avoidance of temperature-conserving methods so that babies on the operating table are allowed to cool spontaneously (the authors have apparently not tried to cool them more than this actively), the maintenance of their infants in incubators at 85° F., 100 per cent humidity in the atmosphere, the rigorous avoidance of overhydration, even the general avoidance of saline solutions more concentrated than N/5.

Atlas de Colposcopie. By Gustav Mestwerdt. Second edition, 164 pages, 151 illustrations. Paris, 1955, Masson & Cie. 3,600 fr.

For many years, the European gynecological clinics have used the colposcope rather extensively in the diagnosis and evaluation of lesions of the uterine cervix. It is interesting to note that this method of study has not been widely accepted throughout the United States. This is due in large part to the lack of familiarity with the technique, as well as the failure of the physician in the country to appreciate the value of the colposcope as a diagnostic tool. In *Atlas de Colposcopie* Dr. Mestwerdt graphically portrays the many lesions of the uterine cervix available for study by the colposcope. He correlates the view through the colposcope with the gross appearance as well as the microscopic picture on biopsy.

The atlas is really quite well done and beautifully illustrates what a skilled individual may learn through the colposcope if he elects to spend the time necessarily associated with its routine use.

Martius' Gynecological Operations. Translated by Milton McCall and Karl A. Bolten. 397 pages, 450 illustrations. Boston, 1956, Little, Brown & Company. $20.00.

One of the world's foremost texts on operative gynecology has been translated into English for the second time. The former translation was of the first edition of the work and appeared in this country in 1939, published by S. B. Debour, under the editorship of W. A. Newman Dorland. Neither the translation nor the format was particularly pleasing. It was, however, immediately apparent that, in spite of these shortcomings, here was a text on operative gynecology of unusual merit and clarity.

The new translation by McCall and Bolten of Martius' seventh edition is worthy of the high caliber of the text. The English is clear, concise, and idiomatic. The sentence and paragraph structure is natural and not that of word-for-word translation. The elimination of the long redundant sentences has, in spite of added material, saved approximately 60 pages over the previous translation.

The illustrations have been reproduced with splendid clarity and in pleasing color. These are perhaps worth a word of comment. They are semidiagrammatical rather than artistic and do not possess either the finish or anatomical perfection shown in some of our operative texts. And yet so well do they demonstrate the where and how of gynecological operations that they are virtually unsurpassed in the field.

One must anticipate a certain degree of ethnocentricism in any text. In this one it appears as a limitation of worldiness of reference, in the use of certain operations no longer widely in vogue, and in the omission of others. However, in the portrayal of operations commonly employed in the specialty of gynecology, the volume takes its place with the splendid English and American operative texts of Shaw and Te Linde.

Carcinoma of the Breast. By Andrew G. Jessiman and Francis D. Moore. 135 pages. Boston, 1956, Little, Brown & Company.

This little book is in capsule form a review of some of the problems of cancer of the breast. The authors have deliberately omitted a discussion of the relation of cancer of the breast to benign breast disease. As might be expected, interest is heavily weighted toward the endocrine factors involved in the study and treatment of cancer of the breast. The book is necessarily didactic and superficial, but it forms an interesting review. The authors appear to prefer hypophysectomy to adrenalectomy for advanced cancer in metastatic disease, and favor prophylactic castration in women in the menopausal or premenopausal age group. There are only a few words devoted to the operation for cancer of the breast; they are the questionable statements that excisional biopsy is safer than incisional biopsy, and the obviously dangerous statement that "when cancer is obvious by all physical signs and characteristic metastases are present we should not endanger the patient by a compulsive desire for immediate histologic proof." It is precisely this reasoning which from time to time leads to a radical mastectomy for an abscess of the breast. The authors favor the standard radical mastectomy as opposed to McWhirter's simple mastectomy with x-ray therapy, with respect to which they accept Ackerman's criticisms and they are confident that the extended operations have little to offer.

No space is devoted to operative technique.

Equilibrio endocrino in gravidanza. Second Report of the Sixth National Congress of the Italian Society of Endocrinology. By F. Vozza, G. Nicora, and F. E. Mansani. 295 pages, 45 illustrations. Parma, 1957, Scuola Tipografica Benedettina.

A wealth of material concerning the three endocrine glands immediately associated with pregnancy is contained in this little book. It is divided into several main sections which deal with the hypophysis, the placenta, the ovary, estrogens, progesterone, and relaxin. After a brief résumé of the anatomical features of the various glands is presented, special reference is made to the changes related to pregnancy. The chemistry and physiological action of the various hormones are reviewed in the light of recent experimental work, both animal and human. At the end of the book a critical summary of various chapters is given. An extensive bibliography is given at the end of each chapter. There are several poorly reproduced colored plates of histological sections but aside from this the small book offers an adequate summary of current knowledge concerning the hypophysis, placenta, and ovary, and their hormones in relation to pregnancy.

The Physician-Writer's Book: Tricks of the Trade of Medical Writing. By R. M. Hewitt. 415 pages with illustrations. Philadelphia, 1957, W. B. Saunders Company. $9.00.

The Physician-Writer's Book discusses selection of title and subject, style of writing, preparation of manuscript, use of illustrations, and method of securing copyrights. The book minutely reviews words and phrases frequently misused by the physician. Because of its conversational style, the book is easily read from cover to cover. Its use as a handy reference is somewhat limited because of the selection of center heads such as "Finally," "A Trick of the Trade," and "A Prized Memory."

The author is qualified to write such a book because of his past experience as assistant editor of the *Journal of the American Medical Association* and present experience as Senior Consultant of the Section of Publications of the Mayo Clinic.

BOOKS RECEIVED

The following books have been received. Selected reviews will appear in later issues.

Chemistry and Biology of Purines. By G. E. W. Wolstenholme and C. M. O'Connor. 327 pages, 124 illustrations. Boston, 1957, Little, Brown & Company. $9.00.

Obstetrical Nursing. By C. C. VanBlarcom and Erna Ziegel. Fourth edition. 855 pages, 205 illustrations, New York, 1957, The Macmillan Company. $6.50.

Practical Gynecology. By W. J. Reich and M. S. Nechtow. Second edition. 648 pages. Philadelphia, 1957, J. B. Lippincott Company. $12.50.

Synopsis of Obstetrics. Jennings Litzenberg and Charles McLennan. Fifth edition, 403 pages, 163 illustrations. St. Louis, 1957, The C. V. Mosby Company. $6.00.

Regulation and Mode of Action of the Thyroid Hormones, Volume 10. By G. E. W. Wolstenholme and E. C. P. Millar. 311 pages, 114 illustrations. Boston, 1957, Little, Brown & Company.

Therapeutic Exercise for Body Alignment and Function. By M. Williams and C. Worthingham. 127 pages. Philadelphia, 1957, W. B. Saunders Company.

SELECTED ABSTRACTS*

British Medical Journal

Volume 1, May 11, 1957.

Marshall, R. J., and Pantridge, J. F.: Mitral Valvotomy During Pregnancy, p. 1097.

Volume 1, May 18, 1957.

Barnes, J., Boutwood, A., Haines, E., Lewington, W., Lister, E., and Haram, J.: Oral Treatment of Trichomonas Vaginitis with Aminitrozole, p. 1160.

The Lancet

Volume 1, January 19, 1957.

*Roberts, H., Kane, K. M., Percival, N., Snow, P., and Please, N. W.: Effects of Some Analgesic Drugs Used in Childbirth With Special Reference to Variation in Respiratory Minute Volume of the Newborn, p. 128.

Roberts, Kane, Percival, Snow, and Please: Effects of Analgesic Drugs Used in Childbirth with Special Reference to Variation in Respiratory Minute Volume of the Newborn, p. 128.

A preliminary survey indicated that Pethidine has a depressant effect on the minute volume of the newborn infant. This volume was recorded by means of a trip spirometer

*Titles preceded by an asterisk are abstracted below.

according to the method of Donald and Lord (Lancet 1: 9, 1953.) The antagonist, levallorphan, did not appear to impair the analgesia when it was given either about an hour before delivery or three-fourths to one hour after the Pethidine, and in the preliminary survey the antagonist appeared to reduce the incidence of anoxia in the newborn babies.

In the main survey 508 patients were studied. One hundred seventy-seven received Pethidine and gas and air (Group A), 178 received levallorphan in addition (Group B), 120 received methylpentynol and gas and air (Group C) and 33 required Pethidine in addition to the methylpentynol (Group C2). In Group A, 150 mg. of Pethidine was given intramuscularly initially and 100 mg. when required. In Group B, the patients received initially 1 mg. levallorphan with 150 mg. Pethidine in the same syringe and later 0.5 mg. with 100 mg. Pethidine. In Group C, the patients received 6 drams of an elixir orally and in Group C2, 150 mg. Pethidine was added. In Group A, anoxia at birth was severe in 6 instances, moderate in 13, and mild in 11, whereas, in Group B, there were no instances of severe anoxia, 7 of moderate, and 15 of mild. In both groups about 4.5 per cent of the mothers had poor relief from pain and somewhat over 70 per cent good. In Group A, 10 of 107 babies had anoxia when Pethidine was given within 3½ hours of delivery, but 11 of 49 babies had anoxia when the drug was given more than 3½ hours before delivery. In Group B, 9 of 104 babies had anoxia when the drug was given within 3½ hours of delivery and 7 of 42 when the drug was given before this time.

The minute volume was recorded in 419 infants and those in each group were approximately the same weight and age. After conversion to a logarthmic scale, the geometric mean was obtained. In Group A, the mean minute volume was 837 ml. if Pethidine was given less than 3½ hours before delivery and 778 ml. if given more than 3½ hours. In Group B, these values were 843 ml. and 827 ml. In Group C, the mean minute volume was 939 ml. and in Group C2, 718 ml. These values were compared to the mean minute volume of 1111.8 ml. (standard deviation 419.9, standard error of the mean 17.7) that was found in 565 infants whose mothers received gas and air anesthesia only.

Pethidine therefore appeared to reduce the minute volume by 10 to 15 per cent. Levallorphan did not influence this minute volume. In the pilot study when larger doses of Pethidine were used, however, levallorphan did seem to have a beneficial effect. Methylpentynol gave satisfactory relief from pain in 66.6 per cent of the instances it was used. This percentage was increased to 72.7 when Pethidine was added to the regimen but when this was done the minute volume of the infants was lowered significantly.

DAVID M. KYDD

Volume 1, April 6, 1957.

*Harvey, C., and Jackson, M. H.: Intermittent Methyltestosterone Therapy in Male Subfertility, p. 711.

Cort, R. L., and Cort, J. H.: Uterine Electrolytes in Pregnancy and Labor, p. 718.

Harvey and Jackson: Intermittent Methyltestosterone Therapy in Male Subfertility, p. 711.

Two groups of subfertile married couples were compared. The 539 husbands in Group I received no therapy beyond vitamin E which is now known to have no detectable effect on fertility. The 148 husbands in Group II received 10 mg. of methyltestosterone sublingually each day between the sixth and sixteenth days of the wife's menstrual cycle. If no conception took place after 4 to 12 cycles, the drug was discontinued either altogether or for several months, the course then being repeated, sometimes in higher dosage. The semen was examined in all cases by the method of Harvey and Jackson (Lancet 2: 134, 1945) and the fertility index was calculated by the method of Harvey (J. Clin. Path. 6: 232, 1953). The fertility indices varied from less than 1 to over 100. Where greater than 50, the chance of conception was considered to depend upon the wife's fertility. When the fertility index of the semen fell below 30, the husband's fertility was considered to be critical.

In Group I there were 51 husbands whose fertility index was less than 10, and 4 wives became pregnant within 2 years (8 per cent), whereas in Group II, there were 39 husbands whose fertility index was less than 10, and 16 wives became pregnant (41 per cent). If the fertility index of the semen was between 10 and 29, 20 of 90 wives (22 per cent) in Group I and 19 of 54 wives (35 per cent) in Group II became pregnant. When the fertility index was found to be between 30 and 49, 49 of 112 wives (44 per cent) in Group I and 9 of 33 wives in Group II became pregnant. When the fertility index was greater than 50, conception occurred in 129 of 286 wives (45 per cent) in Group I and in 11 of 22 wives (50 per cent) in Group II. About half of the 55 pregnancies which occurred in Group II began during the first 6 months of treatment with methyltestosterone; the remainder were distributed fairly evenly over the following 18 months.

Forty-eight of the 93 husbands in Group II who had fertility indices of less than 30 submitted samples of semen after they had received some treatment with methyltestosterone. Among these there were 17 successful donors whose wives conceived and in 11 of these the semen fertility index increased. Of 31 unsuccessful donors, improvement in the fertility index was shown in only 12. An improvement in sperm density and sperm motility was apparently somewhat more marked in the successful donors. There was no change in the volume of the ejaculate in the few instances in which this was measured. The statement is made that the fructose and citric-acid levels were determined and that treatment did not produce any significant alterations. However, no values are given.

That 35 of the 93 wives whose husbands' semen had a fertility index below 30 became pregnant after the husband was treated with methyltestosterone, but only 24 of the 141 wives whose husbands' semen had a similarly low fertility index and whose husbands did not receive methyltestosterone suggested that this drug caused significant improvement. Analysis of the semen after treatment shows that the hormone is not a cure for testicular deficiency but a stimulus to produce the best possible ejaculate.

DAVID M. KYDD

Volume 1, April 13, 1957.

*Bromberg, Y. M., Salzberger, M., and Abrahamov, A.: Fetal Blood in Genital Hemorrhage Due to Placenta Previa and Abruptio Placentae, p. 767.

Bromberg, Salzberger, and Abrahamov: Fetal Blood in Genital Hemorrhage Due to Placenta Previa and Abruptio Placentae, p. 767.

The fetal hemoglobin in the clotted venous blood of 113 healthy pregnant women at term was found to be 0.3-2.3 per cent (mean 1.4 per cent, standard deviation ±0.53, and standard error ±0.081). In 5 instances of placenta previa and in 2 instances of abruptio placentae the fetal hemoglobin in clotted blood expelled from the uterus varied from 2.1 to 4.3 per cent, whereas the fetal hemoglobin in the maternal venous blood varied from 1.1 to 2.3 per cent. In each instance the percentage of fetal hemoglobin in the expelled blood was higher than in the same mother's venous blood and this difference amounted to from 0.8 to 2.3 per cent.

The conclusion is that fetal as well as maternal blood is lost in the course of hemorrhage due to placenta previa or abruptio placentae. This loss from the fetus is usually small, however, no more than 3 to 4 ml. per 100 ml., and not enough to cause anemia of the newborn. However, when the cord has a marginal insertion a considerable loss of blood from the fetus is possible.

DAVID M. KYDD

New England Journal of Medicine

Vol. 254, June 14, 1956.

*Graham, J. B.: Treatment of Choice in Cancer of the Uterine Corpus, p. 1112.

Graham: Treatment of Choice in Cancer of the Uterine Corpus, p. 1112.

Graham quotes data from the literature to indicate that there is no significant difference in the cure rate in carcinoma of the uterine corpus treated by combined irradiation

and surgical methods as compared with the cure rate achievable by hysterectomy alone. In a series of 518 patients, hysterectomy alone achieved a 5 year cure rate of 70 per cent, while in a similar series preoperative irradiation followed by hysterectomy resulted in a 64 per cent cure rate. The author suggests that although this apparent advantage of surgery alone may be only the result of selection, nevertheless, the failure of preoperative radiotherapy to achieve a clear advantage is damaging to the routine use of that technique because the increased expense in time, money, and discomfort can be justified only by distinct improvement in the cure rate.

DOUGLAS M. HAYNES

Vol. 255, August 30, 1956.

*Field, M. G.: The Re-legalization of Abortion in Soviet Russia, p. 421.

Field: The Re-legalization of Abortion in Soviet Russia, p. 421.

In Soviet Russia, four periods can be recognized in which different legislation on abortion was in force. The first period was that between 1917 and 1920 when the Czarist prohibition of abortion on any grounds was in force. In 1920, a law legalizing abortion by doctors in hospitals was adopted. As a result, the proportion of abortions to births increased, but the rate of incompleted abortions presumed to have been secretly performed decreased from 46 to 20 per cent. In 1936, public opinion as reflected in letters to the press was against repeal of the abortion law, but the law was repealed nevertheless. From 1936 to 1955, along with prohibition of abortions, there was legal provision for increasing state aid to mothers. Medical indications listed in the law were very numerous, however, including epilepsy, corneal diseases, narrow pelvis with conjugata vera of 7.5 cm. or less, or other pelvic deformities which made vaginal delivery impossible. The presence in the father or mother or any of their children of such heredofamilial diseases as hemophilia, idiocy, or schizophrenia were also considered indications. Infection of the pelvis or genitals were legal contraindications. As a result of this legislation, abortions were sent underground, and a flourishing black market in the abortion business developed. This continued throughout the period despite propaganda denouncing abortions as a remnant of capitalistic consciousness. Accordingly, in 1955, there was a repeal of the prohibition of abortions. The prevention of abortions was simultaneously encouraged by glorification of motherhood by the state. The reason for the repeal was the desire to protect the health of women by having abortions performed only under proper hospital conditions. It is clear that in repealing the prohibition on abortions, the Soviet regime has recognized that a substantial number of pregnant women will seek abortions for personal and economic reasons, regardless of political ideology or legal prohibition.

DOUGLAS M. HAYNES

Vol. 255, September 13, 1956.

*Gorbach, A. C., and Reid, D. E.: Hiatus Hernia in Pregnancy, p. 517.

Gorbach and Reid: Hiatus Hernia in Pregnancy, p. 517.

The authors point out that because of the more frequent performance of upper gastrointestinal tract series, hiatus hernia occurring in pregnancy has become much more frequently encountered. This disease occurs in older age groups, and is more often seen in women than in men. It may be that the increased abdominal pressure of pregnancy is responsible for some of the gastrointestinal symptoms in pregnancy due to hiatus hernia. Two clinical forms of the disease are distinguished. A small number of cases are extremely severe, exhibiting a syndrome of sudden acute pain, vomiting, and shock. Many of this small group will die, and at autopsy will show a large foramen of Bochdalek in the left leaf of the diaphragm. The more common type is very much less severe; this is the so-called esophageal hiatus hernia, and is conditioned by the presence of a congenitally short esophagus or an enlarged normal esophageal opening so that the upper part of the stomach comes to lie above the diaphragm. These patients may fail to improve from the

normal morning sickness of early pregnancy and may have a misdiagnosis of hyperemesis gravidarum or other psychiatric disorders. Heartburn is characteristic with onset between the twentieth and thirtieth weeks, and all gastrointestinal symptoms associated with this type of hiatus hernia will be relieved by the third or fourth postpartum day. The authors reviewed 50 cases of persistent gastrointestinal symptoms in the last half of pregnancy, and found that 62 per cent of these patients had esophageal hiatus hernias.

DOUGLAS M. HAYNES

Die Medizinische

Volume 1957, April 6, 1957.

*Jaeger, J.: Cancer Detection With Vaginal Cytology Using Vaginal Tampons, p. 479.

Jaeger: Cancer Detection With Vaginal Cytology Using Vaginal Tampons, p. 479.

The author states that 500 clinic patients had vaginal smears made both with standard techniques and with insertion of vaginal tampons. When tampons were in place from 6 to 12 hours, the results were comparable to those from standard techniques. Since use of vaginal tampons affords a method of extending cancer detection to more women, the author advises that the method be used every six months by women who will not undergo pelvic examinations.

FRANCIS B. O'BRIEN

Surgery, Gynecology and Obstetrics

Volume 103, October, 1956.

*Ireton, R., and Ullery, J. C.: The Management of Ascites With Radioactive Gold, p. 437.

Rubin, I. C., Lisa, J. R., and Trundad, S.: Further Observations on Ectopic Endometrium of the Fallopian Tube, p. 469.

Hunter, R. G., Henry, G. W., and Civin, W. H.: The Cornual Sphincter of the Uterus, p. 475.

Ireton and Ullery: The Management of Ascites With Radioactive Gold, p. 437.

This study evaluates the management by radioactive gold of ascites secondary to malignancy in 35 patients. The 3 males and 32 females had a mean age of 35 years and an age range of 29 to 75. The tumor responsible for ascites varied in site of origin and cell type, but the majority were adenocarcinomas; two thirds of the adenocarcinomas were primary in the ovary. The minimum time of follow-up was two months after cessation of treatment.

The amount of radioactive gold administered varied from 35 to 135 mc. diluted with 100 to 500 ml. normal saline solution. The mixture was instilled through a polyethylene tube placed in the peritoneal cavity at the time of operation or paracentesis. One fourth of the patients showed complete remission and one half, some remission for the period of study.

The conclusions were: (a) The type of tumor was of some importance, since none of the patients with sarcomas had remissions. (b) The size of metastasis, the smaller being more favorable, may be of some significance, although this has not been proved. (c) Any form of treatment received by a patient prior to, during, or after the administration of radioactive gold had little significance in the remission of ascites.

Complications encountered during the study were few; those that could be attributed solely to radioactive gold were uncommon and minor. In view of this, the authors feel that the risk of overtreatment is negligible when compared to possible advantages. They therefore suggest that radioactive gold be used prophylactically, particularly at the time of operation on adenomatous tumors with or without metastasis.

VINCENT TRICOMI

Volume 103, December, 1956.

Posse, N., and Kelly, J. V.: A Study of the Effect of Relaxin on Contractility of the Nonpregnant Uterus by Internal Tocometry, p. 687.

Volume 104, March, 1957.

Bowers, J. E., Moeckel, C. W., Yates, G. L., and Wesson, H. R.: A Study of Bladder Function Following Vaginal Hysterectomy, p. 287.

Jacobs, W. M., Daily, H. I., and Wills, S. H.: The Effect of Hysterectomy on Young Women, p. 307.

Volume 104, April, 1957.

Posner, A. C., Friedman, S., and Posner, L. B.: Modern Trends in the Management of Face and Brow Presentation, p. 485.

Volume 104, June, 1957.

Moore, T. C., Battersby, J. S., Roggenkamp, M. W., and Campbell, J. A.: Congenital Posterolateral Diaphragmatic Hernia in the Newborn, p. 675.

Kistner, R. W., and Duncan, C. J.: An Analysis of One Hundred and Five Radical Hysterectomies at the Free Hospital for Women, p. 733.

Wiener klinische Wochenschrift

Vol. 68, December 14, 1956.

Wiedmann, A.: Concerning Some Drug Side Effects in Dermatologic Therapy, p. 973.

Denk, W., and Karrer, K.: Chemotherapy for Prophylaxis Against Recurrence of Carcinoma, p. 977.

*Rockenschaub, V. A., and Weghaupt, K.: Hyperestrinism? p. 979.

Wenger, R.: The Electro- and Vectorcardiogram in Pulmonary Disease, p. 982.

Rockenschaub and Weghaupt: Hyperestrinism? p. 979.

The authors point out that the term "hyperestrinism" has been much abused. Its vague definition is illustrated by its classification into absolute and relative types. A precise definition of hyperestrinism should imply an abnormally high estrogen level in the peripheral blood. Criteria for judging the magnitude of peripheral estrogen titers are not precise, however. It has been demonstrated that increased estrogenic activity, as demonstrated by genital tissue changes, is not necessarily associated with increased amounts of circulating estrogen; nor are the signs and symptoms described as being due to hyperestrinism pathognomonic or easily correlatable. The authors postulate that hyperestrinism syndromes are due to general ovarian insufficiency of which estrogen deficiency is a part. On the basis of experimental and clinical evidence, they believe that an abnormally marked proliferative effect in genital tissues does not necessarily imply that estrogen deficiency can be ruled out.

DOUGLAS M. HAYNES

Items

Canadian Society for Study of Fertility

The Canadian Society for the Study of Fertility will hold its Annual Meeting in London, Ontario, Canada, on Nov. 8 and 9, 1957. Communications in regard to it may be addressed to Dr. Morris P. Wearing, Secretary-Treasurer, 289 Dufferin Avenue, London, Ontario.

The American Society for the Study of Sterility, Grants-in-Aid

The Ortho and Carl G. Hartman grants-in-aid of the American Society for the Study of Sterility, each of $500, are available for 1958. Applications in triplicate for these two grants-in-aid, including a brief outline of the project, should be sent to the Chairman of the Research Correlating Committee of the American Society for the Study of Sterility, Dr. S. Leon Israel, 2116 Spruce Street, Philadelphia 3, Pa., by Nov. 30, 1957.

American Board of Obstetrics and Gynecology

The following candidates were certified by the American Board of Obstetrics and Gynecology on May 25, 1957:

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1. Goldfarb, A. F., and Napp, E. E.: Use of Methallenestril (Vallestril) in Control of Menopausal Symptoms, J.A.M.A. *161*:616 (June 16) 1956.
2. Schneeberg, N. G.; Perczek, L.; Nodine, J. H., and Perloff, W. H.: Methallenestril, a New Synthetic Estrogen, J.A.M.A. *161*:1062 (July 14) 1956.

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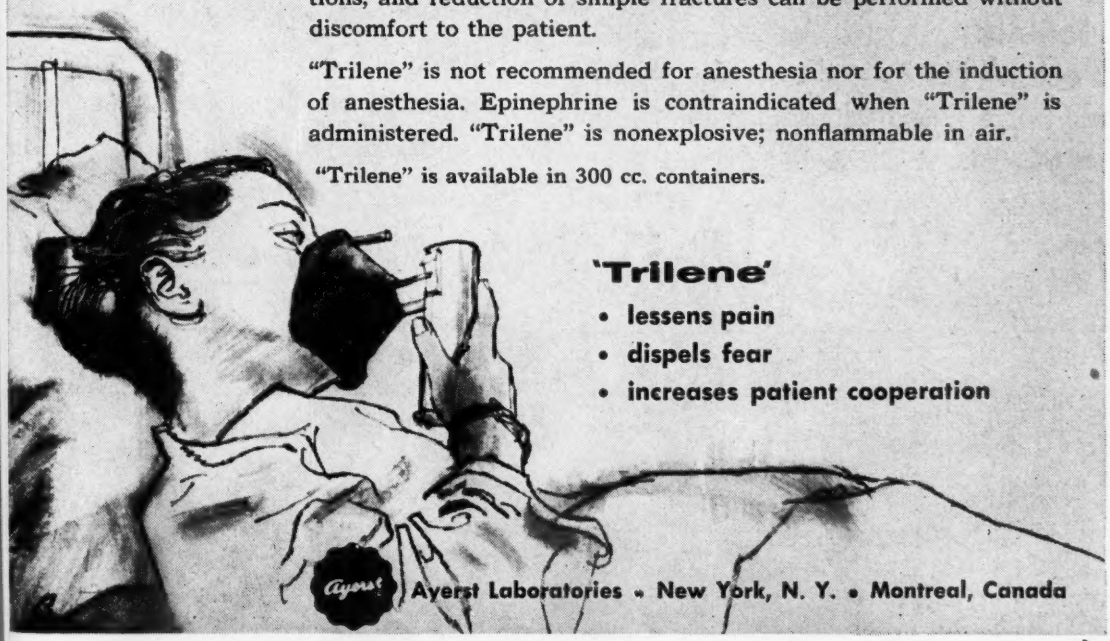

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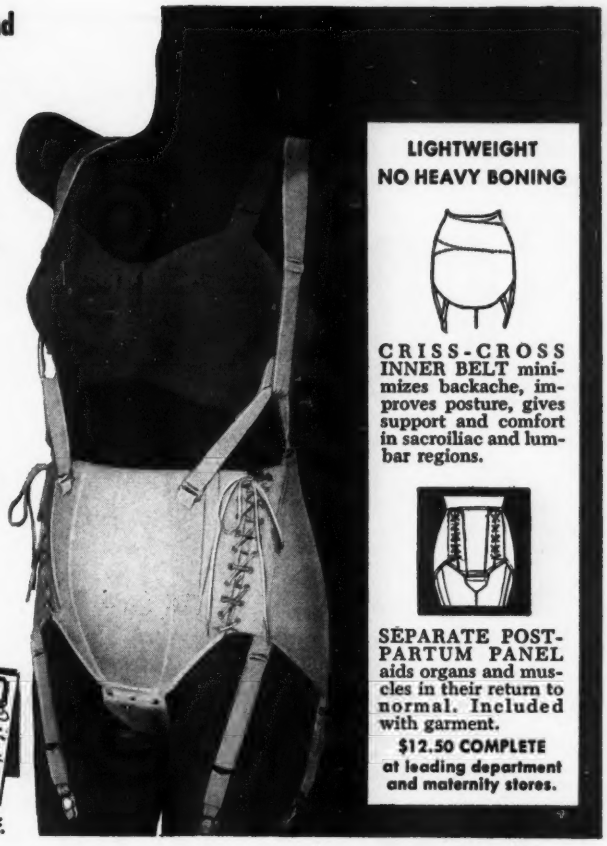
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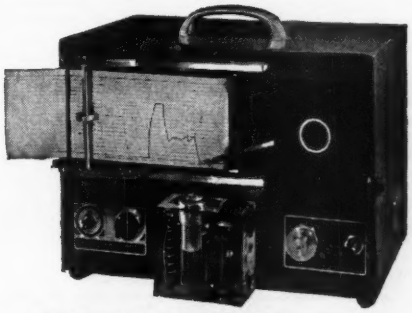

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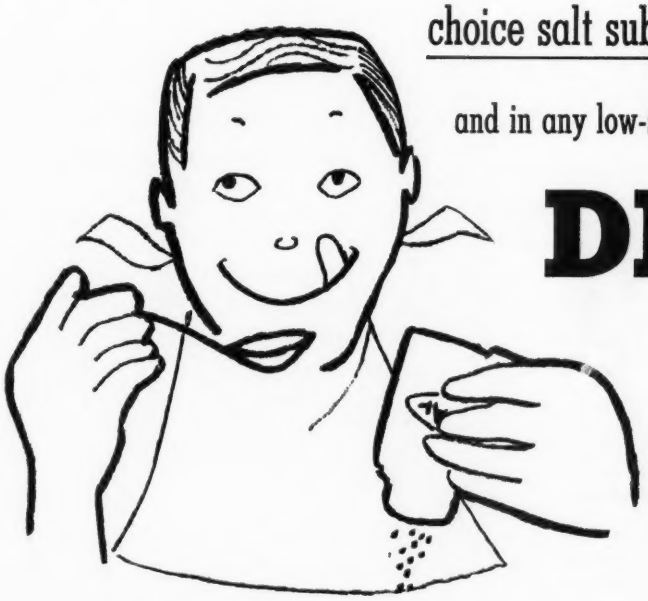

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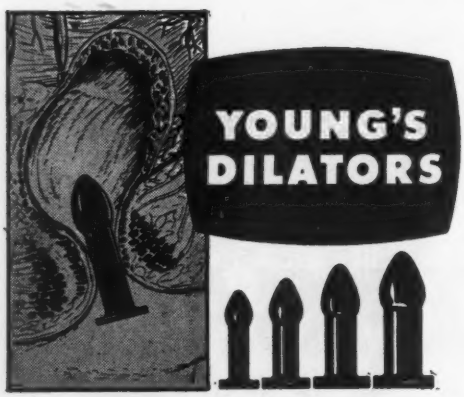

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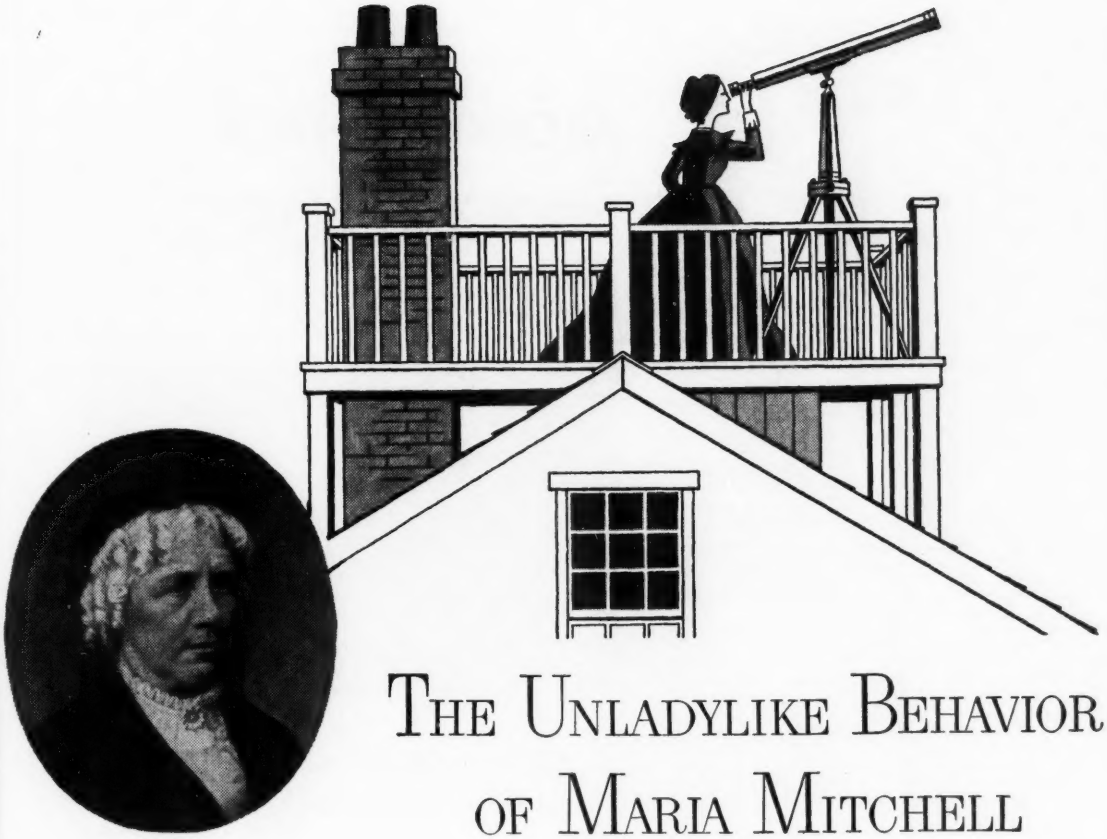

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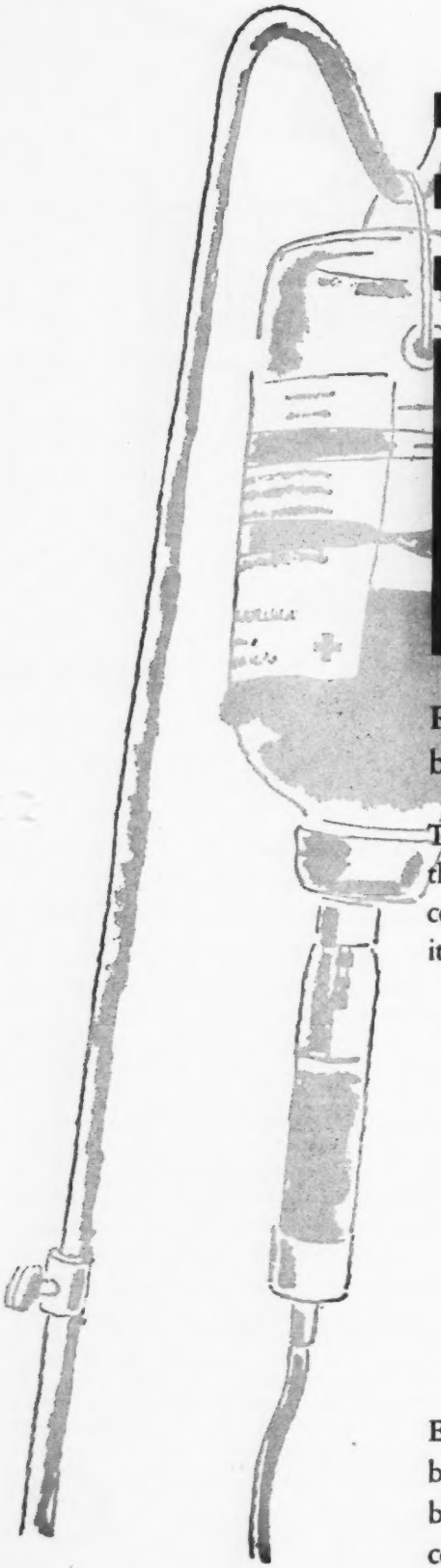

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Caduceus Press ---------- 93
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Ciba Pharmaceutical Products, Inc. -- 61

Davis Company, F. A. ---------- 64
Desitin Chemical Company ---------- 54
Distillation Products Industries ------ 93
Doho Chemical Corporation ---------- 79

Eaton Laboratories ---------- 23, 70, 71
Esta Medical Laboratories, Inc. ------ 76
Ethicon, Inc. --- Insert between pp. 8 and 9

Fesler Company, Inc., The ---------- 12
Fougera & Company, Inc., E. ------ 46, 95

Geigy Pharmaceuticals ---------- 74
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Hoffmann-La Roche, Inc. ---------- 62
Holland-Rantos Company, Inc. ----- 32, 36

Johnson & Johnson (Hospital Division) 17

Kinney & Company, Inc. ---------- 48

Lederle Laboratories ---------- 58, 59
Lilly, and Company, Eli ---------- 84
Linde Air Products Company ---------- 50

Massengill Company, The S. E. ------ ---------- Insert between pp. 44 and 45
Mead Johnson & Company ---------- 29
Merck Sharp & Dohme ---------- 30, 44
Merrell Company, The Wm. S. ------ 9, 52

National Drug Company, The ------ 19, 56
Nu-Lift Company, Inc. ---------- 93

Organon, Inc. ---------- 5, 13
Ortho Pharmaceutical Corporation ---- ----------Insert between pp. 16 and 17
Ortho Pharmaceutical Corporation -- 31, 43

Parke, Davis & Company ---------- ---------- 33, 34, 35, 41, 67, 91, 95
Pet Milk Company ---------- 18
Pfizer Laboratories, Div. Chas. Pfizer & Co., Inc. ---------- 57, 60
Pharmaseal Laboratories ---------- ---------- Insert between pp. 64 and 65
Poythress & Co., Inc., Wm. P. ------- 40

Robins Co., Inc., A. H. ---------- 53

Schering Corporation ---- 24, 25, 38, 39, 83
Schmid, Inc., Julius ---------- 28, 80
Searle & Company, G. D. ---------- ---------- 14, 15, 66, 85, 89
Sklar Manufacturing Company, J. ---- 26
Smith, Kline & French Laboratories -- ---------- 3, 20, 47, 51, 55
Squibb & Sons, E. R. ---------- 82
Strasenburgh Company, R. J. ------ 81, 91
Stuart Company, The ---------- 65

United States Savings Bonds ---------- 99
University of Kansas School of Medicine ---------- 96

Walker Laboratories, Inc. ---------- 102
Wallace Laboratories ---------- 16, 27
Warner-Chilcott ---------- 7
Webster Company, The William A. ---- ---------- Third Cover
Westwood Pharmaceuticals ---------- 86
White Laboratories, Inc. ------ 86, 96, 97
Whittaker Laboratories, Inc. ---------- 89
Williams & Wilkins Company, The --- 92
Winthrop Laboratories ---------- 42
Wyeth Laboratories ---------- 11, 37, 77

Young & Company, F. E. ---------- 96

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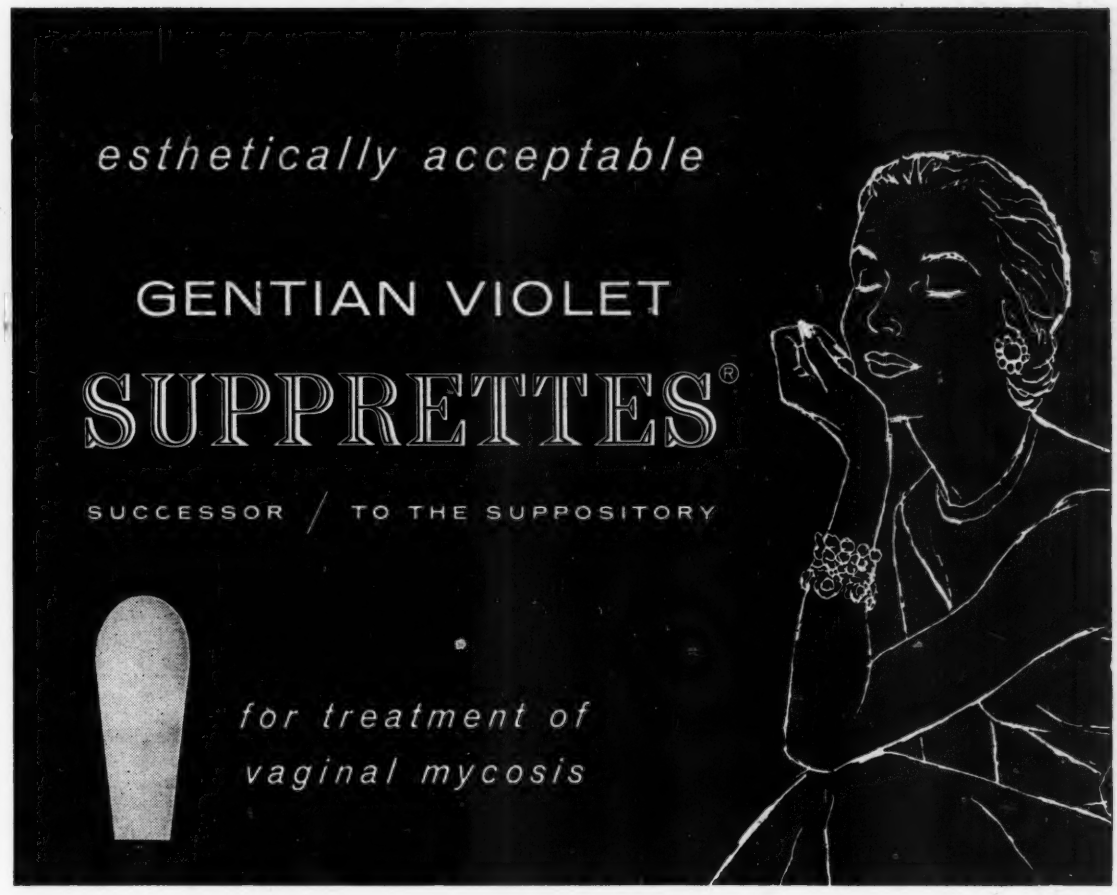

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